

**A Pilot Study of Change in Laryngeal Cough Threshold Sensitivity and PAS
(Penetration Aspiration Scale) Score Within the Acute Stage**

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Abstract

Background: Cough Reflex Testing (CRT) has been shown to be useful in the challenging task of identifying silent aspiration (aspiration without a cough response). With the emergence of the routine clinical use of CRT in the acute stroke population, the following clinical conundrum often arises: Does passing a previously failed CRT mean the risk of silent aspiration has resolved? The purpose of this study was to evaluate the association between change in laryngeal cough threshold sensitivity and change in PAS (Penetration Aspiration Scale) score within the acute stage post-stroke.

Methods: This was a prospective longitudinal pilot study of 20 acute stroke patients utilizing a Cough Reflex Threshold Test (CRTT) at 0.4M, 0.6M and 0.8M citric acid concentrations and Fiberoptic Endoscopic Evaluation of Swallowing (FEES). A cough response threshold was obtained from the CRTT and a PAS (penetration aspiration scale) score from FEES. Inclusion criteria required a PAS score of 4 or above on preliminary FEES or impaired CRT threshold as defined by weak or failed cough test result at 0.8M citric acid concentration. Both test methods were repeated every four days for 20 days or until the participant no longer aspirated/penetrated and had a normal result on CRTT on two consecutive assessment sessions. Agreement between changes in the two tests was evaluated using the Cohen's Kappa statistic.

Results: Eighteen of the twenty participants in this study aspirated on initial assessment, ten of which were silent. One participant continued to aspirate at study completion. On initial assessment eleven participants had a C2 response threshold at 0.4M citric acid concentration and three participants failed to reach threshold at 0.8M citric acid concentration. At study completion, 18 participants had a C2 response threshold at 0.4M citric acid concentration and one participant failed to reach threshold at 0.8M citric acid concentration. During the study, sixty-six re-assessments took place; there were fifteen incidences of improved cough response threshold on re-assessment and thirty-one incidences of improved PAS score. There was no significant agreement between improved laryngeal cough reflex

threshold and improved PAS score during the acute stage Kappa = 0.0598 ($p < 0.0574$), 95% CI (-0.1496- 0.2692).

Conclusion: Significant limitations of this study included small data set and potential flooring effect of the CRT. Due to the limitations of this study, no conclusions can be made as to the appropriateness of reinstating oral intake based on passing a previously failed CRT.

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1.0 Introduction

For healthy individuals the ability to swallow is normally safe and pleasurable. Within this population, the frequency and apparent ease of swallowing often results in an underestimation of the neurological and physiological complexity of swallowing. The oropharyngeal stages of swallowing are complex, highly coordinated and rapid. Early theories pertaining to the neural control of swallowing were largely derived from studies of animal models. However, recent advances in Magnetic Resonance Imaging (MRI), Computerized Tomography (CT) and Positron Emission Tomography (PET) have greatly expanded our knowledge of the neural control of swallowing.

According to the World Health Organization (WHO) (2002), 15 million people have a stroke worldwide each year, of these, five million die and another five million are permanently impaired. In developed countries, the incidence of stroke is declining, largely due to efforts to lower blood pressure and reduce smoking (WHO 2002). However, the overall rate of stroke remains high due to aging of the population (WHO 2002). The medical term used to describe an impairment of swallowing is dysphagia. The term dysphagia derives from the Greek root *dys* meaning difficulty or disordered, and *phagia* meaning "to eat". Dysphagia is a common morbidity of stroke. Patients with dysphagia are at risk of aspiration, i.e. the passage of food/fluid below the vocal folds. As early as the nineteen thirties, Amberson (1937) reported the consequences of aspiration *"The consequences of inhaling various substances into the bronchi and lungs provide a subject for interesting study and vital importance for many patients. Bronchopneumonia is one of these consequences."* J.B. Amberson, 1937.

Aspiration remains the leading cause of death following stroke (Henon, et al. 1995). The potentially fatal consequences of aspiration in this population highlight the necessity of accurate dysphagia identification. Historically, the identification of aspiration was based on the assumption that aspiration results in the elicitation of a cough. It is now widely accepted that this assumption is false. The advent of instrumental methods of dysphagia assessment (Videofluoroscopic Swallow Study (VFSS) and FEES) resulted in the identification of the phenomenon of silent aspiration, defined as

aspiration in the absence of a subsequent cough. Research in the 1990s revealed the relatively high incidence of silent aspiration in the stroke population and in turn highlighted the inability of bedside dysphagia screening to detect this feature of impaired function (Holas, DePippo and Reading 1994 and Daniels et al. 1998). Clinical dysphagia assessments are routinely carried out in many institutions serving the stroke population. However, the inability of a clinical dysphagia assessment to detect silent aspiration results in those patients most at risk of aspiration pneumonia not being detected. The challenge faced by those managing the care of acute stroke patients is complex. The need to provide acute dysphagia assessment, that is reliable in detecting silent aspiration, needs to be balanced with it being financially viable and readily available. Cough reflex testing (CRT) offers great potential in the quest to identify those at risk of silent aspiration. With the emergence of CRT in routine clinical use, many questions are raised as to how to integrate this information into clinical practice.

2.0 Literature Review

2.1 Dysphagia

Stroke is the third greatest cause of death in New Zealand (Ministry of Health 2009). Every year, approximately 6000 New Zealanders will have a stroke (Brown, 2009). Following a systematic review, Feigin, Lawes, Bennett, Barker-Collo, and Parag (2009) concluded that the incidence of stroke in New Zealand is comparatively high in relation to other high-income countries (using World Bank country classification). Lifetime costs per stroke patient in New Zealand are estimated at \$73,600, with a total cost to the country of over \$450 million per annum (Brown, 2009). This is estimated to rise to more than \$700 million by 2015 (Stroke Foundation of New Zealand and New Zealand Guideline Group, 2010).

A major complication of stroke is the inability to safely swallow (dysphagia). The reported incidence of dysphagia varies considerably depending on the definition of dysphagia and the timing and method of assessment. Videofluoroscopic evidence reports the incidence of dysphagia in the acute phase as 78% (Daniels and Foundas, 1999) and 71% (Hamdy et al. 1998). Aspiration is reported in 38% (Daniels and Foundas, 1999) and 42% (Kidd, Lawson, Nesbitt and MacMahon 1993) of dysphagic patients.

The presence of dysphagia increases the risk of poor nutrition, hydration and aspiration-related pneumonia (Martino, et al. 2005). Dysphagia and its associated complications increase the length of hospital admission and are associated with increased mortality, co-morbidities, institutionalization and health care costs (Smithard, et al. 1996). Up to one-third of stroke patients will develop pneumonia (Sellars, et al. 2007) with this providing the greatest contribution to mortality of all medical complications (Heuschmann et al. 2004). Armstrong and Mosher (2011) summarised that pneumonia is often due to aspiration.

Whilst the initial incidence of dysphagia is high, it is widely recognised that for many patients dysphagia is transient and spontaneously resolves. Gorden, Langton, Hewer, and Wade (1987) reported that 86% of stroke patients who were diagnosed with dysphagia on admission were able to safely swallow two weeks later with a mean recovery time of 8.5 days. Hamdy et al. (1998) studied 28 patients following unilateral hemispheric stroke. Dysphagia was initially present in 71% of patients which reduced to 46% at one month post and 41% at three months post. The considerable difference in recovery rates between Gorden et al. (1987) and Hamdy et al. (1998) studies can be largely attributed to different assessment methods and definitions of dysphagia. Hamdy et al. (1998) used a validated tool for swallowing assessment, namely VFSS, and assessed not only aspiration/penetration, but crucially other manifestations of dysphagia. Gorden et al. (1987) utilized a water swallow test and defined dysphagia as “the inability to drink 50 ml water, or choking more than once while attempting to drink 50 ml water on two occasions” (p. 411). The absence of a validated swallowing assessment, a deficient definition of dysphagia, and the reduced value of clinical observational assessment in estimating impairment, significantly limits the usefulness of Gorden et al. (1987) findings.

Whilst the neurophysiology of stroke recovery is not fully understood, recovery in the acute stage is often attributable to the resolution of oedema and return of circulation to the ischemic penumbra (Dombovy, 1991). Hamdy et al. (1998) reported that for post-hemispheric stroke patients with improving dysphagia there was increased pharyngeal representation in the unaffected cerebral hemisphere. However for non-dysphagic and persistently dysphagic patients there was little change in pharyngeal representation in either hemisphere. Hamdy et al (1998) suggest reorganisation of the intact hemisphere as a mechanism for dysphagia recovery.

2.2 Silent Aspiration

Initial assessment of swallowing function is generally completed at bedside. Two key components of the traditional dysphagia assessment are cranial nerve assessment and observation of oral ingestion at bedside. However, research has repeatedly demonstrated that this method of

assessment is not reliable for detecting aspiration (Smithard et al. 1998). Identification of aspiration using non-instrumental methods is based on the belief that a patient will cough when they aspirate. However, many studies have proven this belief to be false, with clinical assessment complicated by the phenomenon of “silent aspiration”, a term coined by Linden & Siebens (1983). Silent aspiration occurs when food, fluid or saliva is aspirated below the level of the true vocal cords, and no cough is triggered. Whilst silent aspiration of saliva during sleep is reported to occur in the normal population (Huxley, Viroslav, Gray and Pierce 1978), silent aspiration of food or fluid is considered pathological.

Currently, the only widely recognized methods of detecting silent aspiration are VFSS and FEES. Langmore, Schatz, and Olson (1988) are generally recognized as producing the first published description of the procedure they termed “FEES”. FEES is carried out by introducing a flexible endoscope transnasally into the hypopharynx, enabling the pharyngeal and laryngeal structures to be viewed. FEES is unable to provide information on oral and oesophageal function and provides only limited information on swallowing physiology. Therefore, VFSS remains the gold standard for swallowing assessment (RSCSLT 2005). FEES however has proven itself to be a valid (Colodny, 2002; Langmore, Schatz & Olsen, 1991; Perie et al. 1998; Wu, Hsiao, Chan, Chang, & Lee, 1997), easily accessible (Bastian 1993), cost effective (Ajemian, Nirmul, Anderson, Zirlen & Kwasnik 2001) and repeatable tool (Bastian 1993) for identifying the presence of audible and silent aspiration. FEES is a safe procedure with low incidence of complications (Aviv & Johnson, 2000; Langmore, 2001) and has received increasing support for its use in acute dysphagia assessment, specifically in the acute stroke population (Leder & Espinosa, 2002).

Historically, the frequency of silent aspiration has been likely underreported due to insensitive methods of identification. Garon, Sierzant & Ormiston (2009) carried out a retrospective study of silent aspiration rates of patients referred for VFSS. Seventy-nine percent of the 58 patients with brainstem stroke aspirated silently; 51% of the 107 right hemisphere stroke patients aspirated silently

and 40% of the 109 left hemisphere stroke patients aspirated silently. Whilst this information is useful, the rates of silent aspiration can not be generalised to the stroke population as a whole. Given the study population included only patients referred for VFSS, it is plausible that for many patients a suspicion of silent aspiration triggered the VFSS, and therefore the rates of silent aspiration may be exaggerated. Alternatively, it could be argued that rates of silent aspiration may be underestimated as silent aspirators were not detected on clinical exam and therefore were not referred for VFSS. Holas, et al. (1994) studied 114 stroke patients undertaking rehabilitation. The median time from stroke to VFSS was four weeks. They reported that of the 53% of patients that aspirated, 72% did so silently with 39% of all participants observed to silently aspirate. The precursor to carrying out a VFSS in this study was a failed bedside swallowing assessment. Therefore, whilst the rates for silent aspiration appear high, it is possible that the silent aspiration rates were indeed even higher due to the poor validity of bedside assessment in detecting silent aspiration.

Daniels et al. (1998) studied 55 consecutive stroke patients using VFSS. VFSS was carried out within five days of stroke. Thirty eight percent aspirated, of these 67% did so silently, with 25% of all participants observed to silently aspirate. Daniels et al. (1998) eliminates some of the bias of previous studies by carrying out a valid swallowing assessment for detecting silent aspiration on all patients admitted with a diagnosis of stroke. However whilst the participant population is acute, one could argue that as VFSS was carried out up to five days post-stroke the initial rates of aspiration could have indeed be significantly higher. Holas et al. (1994) additionally demonstrated the associated risk posed for patients that silently aspirate. Holas et al (1994) reported 5.5 times greater risk for developing pneumonia for stroke patients that aspirated silently, compared with those who coughed when they aspirated or those that did not aspirate. Holas et al (1994) study highlights the critical clinical need of being able identify those at risk of silent aspiration post-stroke.

2.3 Cough

Many researchers have demonstrated an association between impaired cough and dysphagia following a stroke (Daniels, McAdam, Brailey, & Founders, 1997; Daniels et al. 1998; Smithard et al. 1998; Smith Hammond et al. 2001). The European Respiratory Society (ERS) recommended two possible definitions of cough. Firstly, Korpas & Tomori (1979) defines cough as “a three-phase expulsive motor act characterized by an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) and then by opening of the glottis and rapid expiratory airflow (expulsive phase)” (*pg 1258* cited ERS). This definition appears in many textbooks, frequently with a fourth ‘recovery phase’ (the deep inspiration that usually follows a cough). The second definition recommended by the ERS is proposed by Morice, McGarvey & Pavord (2006). They define cough as a forced expiratory manoeuvre, usually against a closed glottis and associated with a characteristic sound” (*pg 5*). Morice et al. (2006) argue that whilst the first definition might be appropriate for laboratory and analytical studies, the second is more appropriate for clinical use, where a fully closed glottis cannot be presumed. Wilkins, Stoller, & Kacmarek (2009) report that the compressive phase is typically 0.2 seconds and alveolar pressures often exceed 100mm Hg. In the expulsive phase air flow from the lungs during cough can reach velocities as high as 500 miles per hour (Wilkins et al. 2009).

Whilst a cough is frequently referred to as a reflex, a reflex is typically thought to be a rapid, immediate involuntary reaction to a stimulus below the level of consciousness. Humans have the ability to produce both a voluntary and involuntary (reflexive) cough, as well as being able to exert some cortical modulation over a reflexive cough (Widdicombe, Eccles, & Fontana 2006). Using healthy participants and inhaled citric acid, Leow, Huckabee, & Anderson (2006) reported significantly higher cough thresholds during suppressed cough compared to the threshold that triggered a spontaneous cough, thus demonstrating the capacity for cortical control of reflexive cough. Therefore it can be argued that in its purest sense, a cough is not a true simple reflex, but a more complex reflex.

Fontana (2008) highlights the distinction between cough as described above by Korpas et al (1979) and the expiration reflex (ER) also called the laryngeal expiration reflex (LER) by Widdicombe, Addington, Fontana and Stephens (2011). The ER occurs in the absence of the initial inspiratory phase (Fontana, 2008). Cough is responsible for clearing lower airways from debris and mucus whereas the ER is thought to be responsible for preventing aspiration. The absence of the inspiratory phase occurs presumably to prevent material from being inhaled further into the lungs, resulting in ER being referred to as “anti-aspiration” (Widdicombe et al 2011, p.312).

The ER was first described by Williams in 1841 (cited by Fontana 2008). The ER is triggered by mechanical or chemical irritation of the vocal folds or trachea. Different neural mechanisms have been identified between cough and ER (Shannon et al. 2004). Whilst the differentiation of cough verses ER is clearly important, Widdicombe & Fontana (2006) acknowledge that clinically cough and ER rarely occur in isolation.

2.4 Cough Receptors

In order for a reflexive cough or ER to occur an airway irritant must first be detected. There are reported to be many types of afferent receptors in the airways. There are at least five noted to be in the larynx: pressure, drive, cold, irritant and C-fibres. The trachea and bronchi are reported to contain at least four: slowly and rapidly adapting stretch receptors (SARs and RARs), C-fibre receptors, and those in neuroepithelial bodies (Widdicombe 2001). In 1926, Keller & Loeser (cited by Chang & Widdicombe 2007) first proposed the theory of distinct cough receptors. Although this theory has been widely assumed to be correct it has only recently been proven (Canning et al. 2004). Mechanoreceptors which are sensitive to pressure and chemoreceptors which are sensitive to chemical irritants are the two types of receptors thought to be responsible for cough (Mokry & Nosalova 2007). Whilst it is acknowledged that there are several afferent receptors in the larynx, the

focus of this discussion is on cough receptors, therefore only mechanoreceptors and chemoreceptors are explored in further detail.

Mechanoreceptors and chemoreceptors are dispersed throughout the larynx and tracheobronchial tree (Mokry & Nosalova 2007). These cough receptors are also evident in non-respiratory areas such as the proximal oesophagus, external auditory meatus and tympanic membrane (Fontana & Lavorini 2006). Mechanoreceptors respond to mechanical pressure or distortion, including lung inflation, bronchospasm or light touch (Mazzone, 2005). Mechanoreceptors typically do not respond to chemical stimulation unless the chemical causes a mechanical distortion of the nerve terminal (Bergren, 1997). Chemoreceptors, also referred to as C-fibres or nociceptors, respond to a chemical substance but do not typically respond to mechanical stimulation (Canning, Reynolds, & Mazzone 2001; Ho, Gu, Lin, & Lee 2001).

2.5 Neurophysiology of Reflexive Cough

Stimulus from a chemical or mechanical irritant that crosses the sensory threshold of the cough receptors will result in afferent nerves discharging an action potential. Sensory information from cough receptors in the larynx is transmitted via the internal branch of the superior laryngeal nerve (ibSLN); specifically, the middle ramus of the ibSLN (Kiray, Naderi, & Korman, 2006). More distal receptors in the tracheobronchial tree and pleura are innervated by the recurrent laryngeal and pulmonary branches of the vagus nerve (Widdicombe, 1998). The information then passes to second order neurones in the nucleus tractus solitarius (NTS) located in medulla and lower pons (Mazzone & Geraghty, 2000). There, second order neurones reorganise the primary sensory information and transmit the modified information to the central respiratory generator (CRG) (Bonham, Sekizawa, Chen & Joad 2006). Bonham et al. (2006) describes the CRG as a “group of synaptically connected respiratory related neurones in the ventrolateral medulla” (*pg.313*). The CRG coordinates the activity of the medullary respiratory premotor neurones and motor neurones (Bonham et al. 2006). An action potential is carried via the efferent nerves to the effector organs, leading to the co-ordinated motor

output that is collectively referred to as cough (Lee & Undem, 2008). Shannon, Baekey, Morris, & Lindsey (1998) suggest that it is the short term plasticity of the brainstem networks, specifically the CRG which is responsible for generating normal respiration, that enables cough production. Bonham et al (2006) describes the nature of this plasticity stating “*neuronal activity in the CRG is transiently interrupted, perhaps by additional synaptic interactions, transforming it into a central cough generator*” (pg. 313). Morris et al. (2003) refer to the rapid onset of changes in the RPG that occur during cough as reconfiguration. Sensory input from the SLN transmits not only to the NTS, as the primary sensory nuclei, but also transfers directly to the nucleus ambiguous (NA). Miller (1999) describes the NA as one of the cranial motor nuclei of the brainstem with motoneurons that innervate laryngeal, pharyngeal and oesophageal muscles. The transmission of sensory input directly from the SNL to NA, and bypassing the NTS enables a reflexive cough to be produced within milliseconds of the sensory receptors within the larynx being stimulated.

2.6 Dysphagia and Impaired Cough

Whilst an association between impaired cough and dysphagia following stroke has been well reported, less is known as to why this occurs. Following brainstem stroke, impaired cough may occur as a result of damage to afferent and efferent nerves (cranial and spinal nerves) involved in cough. Brainstem stroke may also result in direct damage to the NTS located in the medulla and lower pons or the CRG located in the ventrolateral medulla. Addington, Stephens, Widdicombe & Rekab (2005) introduced the term “brainstem shock” (pg.7) to explain the impaired cough in subjects with cerebral hemispheric stroke. Addington et al (2005) suggest that a downwards pressure and/or mass effects secondary to cerebral edema following stroke could have an adverse effect on vital brainstem functions. Addington et al. (2005) is quoted as defining brainstem shock as a “*global neurological condition involving a transient or permanent impairment of one or more of the following vital functions: the reticular activating system, respiratory drive or the laryngeal cough reflex*” (pg 7). Widdicombe, Eccles, & Fontana, (2006) propose that since coughing increases cerebrospinal fluid

pressure, brainstem shock leading to cough suppression might function to prevent exacerbation of brain injury.

Smith-Hammond et al. (2009) reported that objective measures of voluntary cough can be used to help identify stroke patients at risk of aspiration. However Stephens, Addington, & Widdicombe (2003) concluded that whilst a significant percentage of the 30 stroke patients in their study had abnormal voluntary cough, as a result of what they term “cough apraxia” (p.381), none developed aspiration pneumonia. Stephens et al. (2003) reported intact laryngeal cough reflex in all patients and concluded voluntary cough is of limited use in screening subjects for aspiration pneumonia risk and that the laryngeal cough reflex is more important for airway protection. Widdicombe et al. (2011) suggest that, given the cortico-brainstem control of the voluntary cough, it may not be involved in aspiration prevention.

2.7 Cough Reflex Testing

The Cough Reflex Test (CRT), which has been in use for over 50 years, has been specifically designed to assess reflexive, as opposed to voluntary, cough. The CRT involve an irritant being introduced into the upper airway and the subsequent behavioural response being recorded (Bickerman & Barach, 1954; cited Lin, Lai, Wu, Wang & Wang, 1999). Several tussive agents have been used for cough reflex testing: however Morice, Kastelik, & Thompson (2001) reported that only capsaicin and citric acid are reliable for clinical use due to their reproducibility across time. Whilst chemoreceptors and mechanoreceptors have been identified as cough receptors, the interplay between these receptor types remains unknown in detecting aspiration. Unlike capsaicin, which only activates chemoreceptors (Morice et al. 2001), citric acid has been shown to stimulate both cough receptor types (Mazzone, 2005). This property is clearly advantageous when used to investigate cough that protects against aspiration.

Only in the past 20 years have researchers used cough reflex testing to specifically test cough in the stroke population. Kobayashi, Hoshino, Okayama, Sekizawa & Sasaki (1994) assessed

swallowing and cough reflex in 20 control participants and 10 stroke patients. Cough threshold sensitivity was assessed using citric acid. The swallowing reflex was evaluated using latency response from the time of injecting 1 ml of water into the pharynx via nasal catheter to the onset of swallow. Both the swallowing and cough reflexes were examined once a week for 4 weeks. At 1 week, all participants in the experimental group showed impaired swallowing and cough reflexes. At 3 weeks, swallowing reflex latency had recovered to the same level as the controls. However cough reflex threshold remained abnormally high in the experimental group at weeks 3 and 4 compared to the control group. A significant limitation of this study is the lack of a validated tool to assess swallowing function. Whilst impaired swallowing latency many have resolved in the experimental group during the course of the study, it is not implicit that dysphagia or, critically, aspiration had resolved. Furthermore it is not clear whether Kobayashi et al. (1994) were reliable in testing swallowing latency. Variables such as depth of catheter within the pharynx, angle of distal end of catheter and flow rate of bolus into the pharynx, may have effected swallowing latency, and are not reported to have been controlled. Addington, Stephens & Gilliland (1999a) hypothesised that in the acute post-stroke population it is the absence or delayed recovery of the cough reflex demonstrated in Kobayashi et al. (1994) findings, that is responsible for the increased morbidity and mortality.

In addition to stroke itself, there are a number of additional potential factors which may alter the sensitivity of the cough reflex in the stroke population. These include angiotensin-converting enzyme inhibitors (ACE inhibitors) (Nimmi et al. 2003; Yamaya, Yanai, Ohrai, Arai, & Sasaki 2001), pneumonia (Nimmi et al. 2003), aspiration pneumonia (Sekiza, Ujiie, Itabashi, Sasaki, Takishima & Lack 1990), gastro-eophageal reflux (Pecova, Javorkorva, Kudlicka & Tatar, 2007; Phua, McGarvey, Nhu & Ing, 2010), diabetes mellitus (Behara, Das, Dash & Jindal 1995) and smoking (Lin, Lai, Wu, Wang & Wang 1999). All of the above conditions occur in the stroke population and for many are more prevalent in the stroke population than the non-stroke population, for example smoking (Howard et al. 1998) and diabetes mellitus (Tuomilehto, Rastenyte, Jousilahti, Sarti & Vartiainen 1996).

2.8 Cough Reflex Testing to Identify Pneumonia Risk

More recently researchers have used cough reflex testing in the stroke population to identify patients at risk of pneumonia (Addington et al. 1999a; Addington, Stephens, Gilliland and Rodriguez 1999b; Addington et al. 2005; Wakasugi et al. 2008; Miles, et al. in progress). The first to explore the clinical use of CRT in the stroke population was Addington et al (1999a). Their specific aim was to evaluate the efficacy of testing the laryngeal cough reflex for identifying pneumonia risk in acute stroke patients. Addington et al (1999a) used tartaric acid to test the reflexive cough of 400 patients and compared pneumonia rates to a control group of 204 patients from a sister hospital which did not receive a CRT. All patients underwent a bedside swallowing evaluation. A cough reflex test was administered to patients in the experimental group. Recommendations for oral feeding in the experimental group were based heavily on the outcome of the CRT. Patients with normal cough were fed orally. Those with absent or weak cough received non-oral feeding or a restricted diet. The results demonstrate that, in the experimental group, five out of 400 developed pneumonia (1%) of the 204 patients in the control group examined without the CRT, 27 developed pneumonia (13%) ($p < 0.001$). A significant limitation of the study was the failure to disclose pre-existing pneumonia rate across both sites. Pneumonia rates between hospitals vary widely and are influenced by multiple factors (Flory, Joffe, Fishman, Edelstein & Metlay 2009). There was also an absence of objective definitions for the classification of cough response. There was limited use of instrumental swallowing assessment as only 0.9% of patients received a VFSS. Despite these limitations, this study was the first of its kind to support clinical use cough reflex testing as a potentially useful tool in reducing pneumonia rates in the stroke population.

In a subsequent study, Addington, Stephens, Gilliland and Rodriguez (1999b) investigated the effectiveness of cough reflex testing in evaluating laryngeal cough reflex and the development of aspiration pneumonia post-stroke. There were two phases to the study: phase one compared cough reflex test with VFSS and phase two compared cough reflex test with risk of developing pneumonia. The average duration between stroke onset and cough reflex testing was 12 days. Forty participants

took part in the first phase of the study. Twenty-nine (72.5%) of the participants had a normal CRT. Eleven (27.5%) of all participants had an abnormal cough. Three participants (7.5%) developed pneumonia, all of these had abnormal CRT, but only 1 was seen to aspirate on VFSS. Of the 121 participants in phase two of the study, 102 had a normal CRT and none developed pneumonia. Nineteen of the 121 participants had an abnormal CRT and two of these developed pneumonia. One hundred and thirty one (81%) participants from a total of 161 participants from phase one and two had a normal CRT. None of the participants in the study with a normal cough reflex test developed pneumonia; this was significant at $p < 0.01$. Of the 30 participants (19%) that had abnormal cough reflex tests, five developed pneumonia. Addington et al (1999 b) concluded that the cough reflex test was a reliable indicator for identifying patients at risk of pneumonia. They also concluded that abnormal findings on VFSS were not a consistent predictor for the development of pneumonia, given that in phase one of the study only one of the three patients that developed pneumonia was seen to aspirate. This finding maybe due to the limitation of VFSS, namely it provides a “snap shot” of swallowing function. This “snap shot” typically occurs when the patient is fed in optimal conditions i.e. fully upright, paced feeding and alert. Swallowing function during VFSS may not be representative of what occurs normally during meal times for patients. Alternatively, it could be argued that the absence of VFSS identifying aspiration in two of the three participants that developed pneumonia may not be due to the limitations of VFSS and may have been fully representative of swallowing function. These two patients may have developed general pneumonia versus a specific aspiration pneumonia. This highlights a further limitation of the study that whilst the aim was to look specifically at aspiration pneumonia, their diagnostic criteria encompasses pneumonia of any aetiology.

More recent research by Addington et al. (2005) looked at 818 consecutive acute stroke patients, and the risk of developing pneumonia when comparing site of lesion and status of laryngeal cough reflex. Participants were monitored for the development of pneumonia during their hospital stay of approximately one month. Seven hundred and six (90%) patients had a normal CRT, of which

26 patients (3.5%) developed pneumonia. Eighty-two (10%) patients had an abnormal CRT defined as “weak” or “absent”. Sixty-nine (84%) of the abnormal group had a weak cough of which seven (10%) developed pneumonia and thirteen (16%) had an absent cough of which two (15%) developed pneumonia. The overall pneumonia rate for the abnormal group was 11%. Addington et al. (2005) concluded there was a significant relationship between CRT and pneumonia risk following both brainstem and cerebral stroke.

The studies by Addington et al. (1999a, 1999b and 2005) share many of the same weaknesses. Firstly, it is difficult to evaluate the actual validity of the cough reflex test in predicting pneumonia, as patients who had an abnormal CRT received immediate intervention to reduce the risk of developing pneumonia. Addington et al (1999b) is quoted as saying “*Although this intervention reduced the sensitivity of the reflex cough test results, it was ethically necessary to appropriately care for the patients*” (p.152).

The method of cough test administration may have resulted in a significant percentage of the dysphagic population being excluded from the studies or receiving inaccurate dosage of the irritant. Participants across the studies were required to exhale, then insert the mouth piece, and take a sharp, deep inhalation. Leakage around the mouth piece and puffing the nebulizer were not considered effective inhalations. This may have led to those unable to follow basic commands, or those with oral dyspraxia or labial weakness being excluded. In turn, this potentially resulted in participants with more significant impairments being excluded. Critically, this exclusion of the most severely impaired participants may bias their experimental group to a lower pneumonia rate. The authors do not specify whether a participant was excluded from the study due to being unable to take “effective inhalation”. The tussive agent that was used in the above studies was tartaric acid; however, Morice et al (2001) concludes that this agent is not reliable for clinical use. There was also no rational or normative data given to support the selection of a 20% concentration level.

Wakasugi et al. (2008) are the only researchers that have looked specifically at validating the use of the CRT in detecting silent aspiration. Two hundred and four participants suspected of dysphagia of mixed aetiology (neurological and non-neurological) underwent a cough test and either a VFSS or FEES. The cough test used a citric acid concentration of 1.0 w/v% and was delivered via face mask for 60 seconds. Of the 204 participants, 97 presented with aspiration, of which 84 passed the CRT and 13 failed. Fifty-two participants silently aspirated, 45 of which failed the CRT and 8 of which passed. The sensitivity of the cough test for detection of silent aspiration was reported to be 0.87 with a specificity of 0.89. Wakasugi et al. (2008) concluded that the cough test was useful in screening for silent aspiration. A significant limitation of this study is the selection of citric acid concentration in the absence of normative data on cough reflex sensitivity thresholds. It remains unknown whether the sensitivity of the CRT in this study could be increased with a reduction in citric acid concentration.

In order to enable accurate clinical application, Monroe (2010) aimed to establish the first normative data set for the citric acid using the facemask method. Monroe (2010) studied 80 participants with cough reflex testing at 10 concentrations of citric acid from 0.8 to 2.6M administered via facemask. The majority of subjects (92.5%) triggered a reflexive cough at 0.8M citric acid concentration. Therefore, an acute stroke patient who fails to trigger a cough at 0.8M citric acid concentration is likely to have an impaired cough reflex. However, the author highlights that due to a flooring effect, it is possible that the cough sensitivity threshold of many participants may in fact be lower than lowest 0.8M citric acid concentration tested. Therefore, potentially an acute stroke patient could pass a CRT at 0.8M and still have impaired cough reflex sensitivity if their pre-stroke cough threshold was less than 0.8M. This scenario would result in a false negative result (implying cough reflex is normal when in fact it is impaired). The rationale for the selection of a 0.8M citric acid concentration was based on a small normative data set for cough response to citric acid using mouth piece administration (Leow, Huckabee & Anderson, 2006).

Currently no research has evaluated whether improved cough reflex is indicative of improved functional swallowing post-stroke or vice versa. We know from Kobayashi et al. (1994) that cough and swallowing reflexes improve over time post-stroke but it is unclear how these reflexes relate to functional swallowing safety. Addington et al. (1999a) and Addington et al. (1999b) infer that improved cough reflex is indicative of improved swallowing function whereby, on passing a repeated test, oral intake was reintroduced to the patient that had previously failed a CRT. With the increased use of cough reflex testing in the acute stroke population, the following clinical conundrum often arises: Does passing a previously failed CRT mean the risk of silent aspiration has resolved?

3.0 Research Aim

3.1 Study Aim

The critical question under evaluation is: Is there a correlation between change in C2 response threshold and PAS score? However, due to the limited scope of this pilot study and the constraints of time and participant numbers, this study will focus on agreement between change in C2 response threshold and PAS score in the acute stroke population.

3.2 Alternative Hypothesis

There will be moderate or higher agreement between improved C2 response threshold and improved PAS scores in the acute stage post-stroke.

3.3 Null Hypothesis

There will be no significant agreement between improved C2 response threshold and improved PAS scores in the acute stage post-stroke.

3.4 Justification

Many stroke patients will experience dysphagia. The consequences of dysphagia are serious and increase morbidity and mortality. Silent aspiration occurs in a significant percentage of dysphagic patients post-stroke. The traditional clinical swallowing assessment is not reliable at identifying silent aspiration risk. If the risk of silent aspiration is not identified, patients are unlikely to be referred for instrumental swallowing assessment. Universally recognized instrumental swallowing assessment methods, namely VFSS and FEES, are expensive, frequently have limited accessibility and have associated risk factors which limit the appropriateness of frequent repeatability. VFSS and FEES are also limited in that they only provide a “snap shot” of swallowing and unless aspiration is seen during the assessment time frame they do not provide information on the patient’s potential to silently aspirate.

The CRT may potentially aid the identification of silent aspiration. The CRT is relatively inexpensive and quick to administer. Emerging research is encouraging in terms of the test's ability to potentially reduce pneumonia rates in stroke patients. Addington et al. (1999) has inferred that the CRT has the capacity to indicate swallowing recovery. Patients previously placed nil by mouth (NBM) due to an initial failed CRT in their study were subsequently started on oral trials once they passed a cough reflex test. Oral feeding was started with these patients on the assumption that recovery of laryngeal cough reflex relates directly to safe swallowing function. However, there is no evidence that changes in CRT accurately reflect swallowing recovery.

If the CRT proves a reliable method for indicating swallowing recovery for patients with known dysphagia following stroke, there would be significant benefits to patient comfort and associated healthcare costs. Due to the minimal cost and patient discomfort, the CRT could be frequently repeated. This would prevent patients being unnecessarily kept NBM or prevent the need for unnecessary, costly, uncomfortable or radiation exposing procedures.

4.0 Methodology

4.1 Participants

Research participants for this prospective longitudinal study were identified from a concurrently conducted validation study for cough reflex testing (Miles, Moore, McFarlane, Lee & Huckabee, manuscript in preparation). Potential participants were approached by their ward Speech and Language Therapist (SLT) and provided with verbal and written information about both studies (validation study and longitudinal study) (Appendix I). Participants were invited to read the information sheet and provide written informed consent (Appendix II). When informed consent could not be obtained from a potential participant, due to cognitive or communication restraints, consent was sought by proxy from next of kin (Appendix III).

Included in both studies were inpatients and outpatients referred to SLT for dysphagia assessment. Inclusion criteria required that they be 16 years of age or over and medically stable. Specific inclusion criteria for this longitudinal study were participation in preliminary study, inpatient status, new diagnosis of stroke, PAS score of 4 or above on preliminary FEES or impaired CRT threshold as defined by weak or failed cough test result at 0.8M citric acid concentration (Monroe 2010). Exclusion criteria included patients who were tracheotomised, referred for palliative/comfort care or were not appropriate for endoscopic assessment as per FEES Policy.

4.2 Procedures

The CRT and FEES took place at the participant's bedside on either an acute or inpatient rehabilitation ward. The order of the CRT and FEES was randomised to prevent an order effect. The delay between CRT and FEES was no longer than 30 minutes. The researcher carrying out the CRT or FEES was blinded to the participant's performance on the previous assessment. Data from the initial CRT and FEES were incorporated into the datasets. Participants had a follow up CRT and

FEES every four days for 20 days (maximum six assessment sessions) or until the participant no longer aspirated (PAS score ≤ 3) and had a normal result on CRT on two consecutive assessment sessions.

4.2.1 Cough Reflex Test. Participants were told that they were undertaking a cough test. They were informed that some of the vials contained liquid that would make them cough and some would not. They were asked only to cough if they felt they needed to. All instructions were read from a card to prevent variability in the instructions participants received. When the nebuliser was turned on participants were instructed to breathe normally. Participants who appeared to be holding their breath were in the first instance reminded to breathe normally and in the second instance asked a question in order to attempt to release the breath hold.

Weekly citric acid vials diluted in 0.9% NaCl to obtain 0.4M, 0.6M and 0.8M citric acid concentrations, were prepared by the inpatient pharmacy. The citric acid and saline solution placebos (0.9% NaCl) were delivered to the patient via a facemask attached to a nebuliser. A PulmoMate nebuliser (model 4650I) (DeVilbiss Healthcare LLC, Pennsylvania, US) was used which has a flow output of 8 litres per minute. Participants initially received a placebo to familiarise themselves with the procedure. Participants then received ascending concentrations of citric acid (0.4M, 0.6M and 0.8M citric acid concentration) interspersed with placebos to prevent order effect and intrusion of a non-reflexive cough. A fixed time method was used; the nebuliser ran for 15 seconds with a 60 second interval between each trial to prevent tachyphylaxis. Each concentration was administered three times followed by a placebo.

Presence or absence of cough and a subjective judgement of cough strength (weak/strong) during the 15-second administration period was documented on the data collection form. Coughs that occurred after the 15-second administration period were not included. The participants cough reflex threshold was scored as the lowest citric acid concentration at which the participant coughed (weak or

strong) on at least two out of the three trials (C2 response threshold) (Choudry and Fuller, 2002). If a weak cough or no cough was recorded, the test continued to the next citric acid concentration. The CRT result was recorded on the data collection form. The CRT was recorded using a Flipcam recorder and copied to a DVD labelled with the participant's non-identifiable code. The CRT was second-marked by an assessor blinded to the C2 response threshold already given by the researcher performing the CRT.

4.2.2 Fiberoptic Endoscopic Evaluation of Swallowing (FEES). The FEES assessment was carried out in line with existing hospital FEES Policy. A water-soluble lubricant was applied to the scope to minimise participant discomfort. Topical anaesthetic was not used due to the risk of migration of the anaesthesia and contamination of the pharynx. Comfortable transnasal endoscopy can be performed without the need for topical anaesthetic (Leder, Ross, Briskin, Sasaki 1997). Participants were sitting upright either in a bed or chair. A flexible 3.2 mm diameter video rhino-laryngoscope (Olympus, ENF- V2) was passed through the nose and positioned above the larynx. An integrated light source and video processor (Olympus, OTV-SI) and LCD Monitor (Olympus OEV203) were used to display the image.

Participants received food and fluids of varying volumes and consistencies mixed with blue dye (Hansells Blue Coloring, Old Fashioned Foods Ltd. NZ) to improve visualisation. A set protocol was followed for the administration of oral intake (Appendix IV). Each consistency was trialled three times. The FEES protocol was truncated for safety if a participant demonstrated significant aspiration. The participants received all single sips of fluids via a noney cup. Participants who aspirated or penetrated on single sips of milk were trialled on thickened liquid (Thickened Creamy Base, Mildly Thick Nectar, Flavor Creations Australia). Participants were given smooth pureed fruit via a teaspoon and 2.5 cm squares of cheese sandwich. Continuous sips of 100 mls of milk were typically delivered via a straw; participants unable to use a straw due to inability to generate sufficient inter-oral pressure received continuous sips via a cup.

The FEES was recorded onto a DVD and labelled with the participant's non-identifiable code. Following the examination, the researcher performing the FEES immediately analysed the recording. Penetration/aspiration status was evaluated using the eight-point Penetration-Aspiration Scale (PAS) (Rosenbek, Robbins, Roecker, Coyle & Woods 1996 See Appendix V). The PAS is a validated ordinal scale. A score of 1 indicates no airway invasion (ie, no laryngeal penetration or aspiration). Scores 2 to 3 indicate penetration: a score of 2 indicates that the material is ejected from the airway versus the score of 3 indicating that the material is not ejected. Scores 4 to 8 indicate aspiration: a score of 4 or 5 indicates material contacts the vocal folds: a score of 5 is given if the material is not ejected from the airway. A score of 6, 7 or 8 indicated material has been aspirated below the level of the vocal folds. A score of 6 or 7 indicate audible aspiration: if the cough is effective to clear the aspirated material a score of 6 is given. A score of 8 indicates silent aspiration.

For each consistency, the highest PAS score for each of the three trials was recorded. PAS score were recorded on the data collection form. The FEES recording was second marked by an assessor blinded to the CRT result and the PAS scores already given by the researcher performing the FEES. C2 response threshold and PAS scores from the data collection forms (both first and second markers) were transferred to an Excel database. The database was password protected and only accessible to approved study personnel. All audio-visual DVD recordings and data collection forms were kept in a locked cupboard.

4.3 Analysis of Data

On initial and subsequent re-assessment, individual PAS scores and C2 response thresholds were recorded. The highest PAS score across all consistencies was used as the participants overall PAS. However due to the limited sample population and the nature of the data, the data were recoded, to enable statistical analysis. On re-assessment, data were recoded as “improved” or “not improved” at each follow-up for the two test methods. For the purpose of this study “improved” on the CRT has been defined as a reduction in C2 response threshold. An “improved” PAS score for the purpose of this study has been defined as a reduction in one or more points on the PAS. For both the CRTT and FEES “not improved” pertained to no change in result or a deterioration i.e. increased C2 response threshold or increased PAS score. Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL). The study evaluated the agreement between the two test methods at each participant re-assessment, thus Kappa and its 95% CI was used to measure agreement between change in C2 response threshold and change in PAS score. Landis and Koch (1977) scale of Kappa agreement has been used to interpret the level of agreement (Table 1). A Kappa value of 0.41 or higher was used as a criterion of good agreement.

Inter-rater reliability between the two markers was analysed using percentage agreement for the following; C2 response threshold, cough type at C2 response threshold (weak/strong), PAS score for single sips of thin, thickened fluids, puree, solids, cough response to aspiration (present/absent), strength of cough response to aspiration (weak/strong) and speed of cough response to aspiration (prompt/latent).

5.0 Results

Participants:

For the larger validation study, 50 participants were assessed with a diagnosis of acute stroke. Twenty-nine participants satisfied the criteria for participation in the longitudinal study. Thirteen participants entered the longitudinal study based solely on their abnormal FEES result (PAS score 4 or above), four participants entered solely based on their abnormal CRT (fail or weak response at 0.8M citric acid concentration) and 12 participants entered the study based on both abnormal CRT and FEES result.

Of the 29 who entered the longitudinal study 20 completed (69%). The reasons for withdrawal were as follows: three participants were transferred from the acute hospital either home or to another hospital for on-going care. Two participants voluntarily declined follow up assessment due to discomfort and one participant died as a result of a further stroke. Three participants were withdrawn by the researchers based on the focus of their treatment changing from active treatment to palliative care.

The mean age of the twenty subjects in the longitudinal study was 76 years (range 64-92 years \pm 8.41). Ten of the participants were male and ten were female. All participants were of New Zealand European ethnicity. Sixteen of the participants (80%) had cardiac co-morbidities. Three of the participants (15%) had respiratory co-morbidities. Four of the participants (20%) were taking ACE inhibitors. Only one participant had a previous diagnosis of stroke, the same participant also had a history of dysphagia, which was reported to have resolved. No other participants had a reported or documented history of dysphagia.

All participants were admitted to hospital secondary to acute stroke. Nineteen (95%) of the participants had an ischemic stroke and one (5%) had a haemorrhagic stroke. Three of the participants

with ischemic stroke received thrombolysis. Seventeen (85%) of the participants had cortical strokes of which eight were left hemisphere and nine were right hemisphere. Three (15%) of the strokes were sub-cortical (one Brainstem, one Thalamic and one Cerebellar & Brainstem).

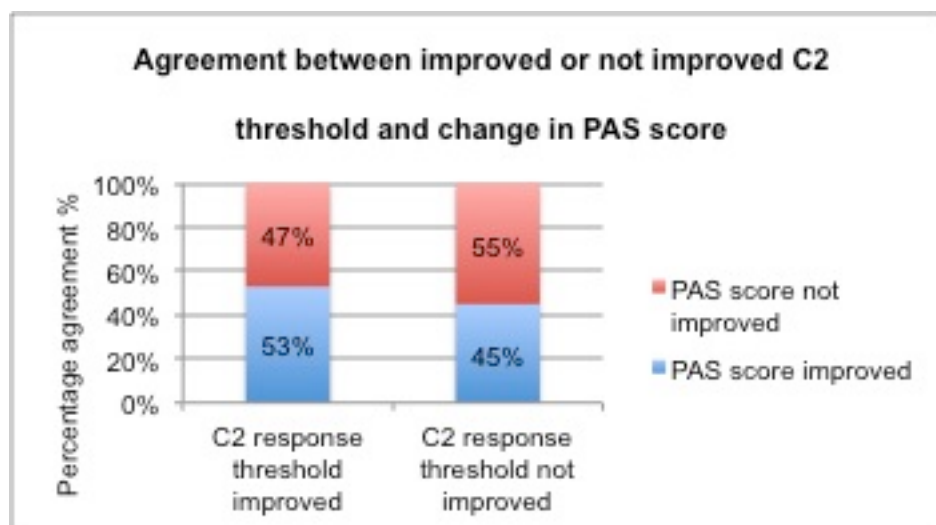
The mean number of days between onset of stroke and initial swallowing assessment was 2.7 days (range 0-10 days \pm 3.03). Initial swallowing assessment was carried out on the day that the patient became alert enough for a swallowing assessment. Three (15%) participants had a diagnosis of pneumonia on entering the study and two participants (10%) were diagnosed with pneumonia during the course of the study. A total of 86 sessions (combined CRT and FEES) were carried out, of these 66 were re-assessments.

C2 Response Threshold and PAS Score:

On initial assessment eleven participants had a C2 response threshold at 0.4M, four participants had a C2 response threshold at 0.6M, two participants had a C2 response threshold at 0.8M and three failed to reach C2 response threshold at 0.8M. On initial assessment 18 of the 20 participants had a PAS score equal or greater than four indicating aspiration, ten of the participants seen to aspirate recorded a PAS score of either 5 or 8 indicating silent aspiration.

C2 response threshold and PAS score for the 20 participants were recorded at each of the 66 follow up assessments (Appendix VI). The agreement between improved C2 response threshold and improved PAS score for the 66 assessments which took place across the maximum of five re-assessment points was not statistically significant, as indicated by Cohen's Kappa = 0.0598 ($p < 0.0574$), 95% CI (-0.1496 - 0.2692). The percentage agreement between "improved" or "not improved" C2 response threshold and "improved" or "not improved" PAS score is presented in figure 1.

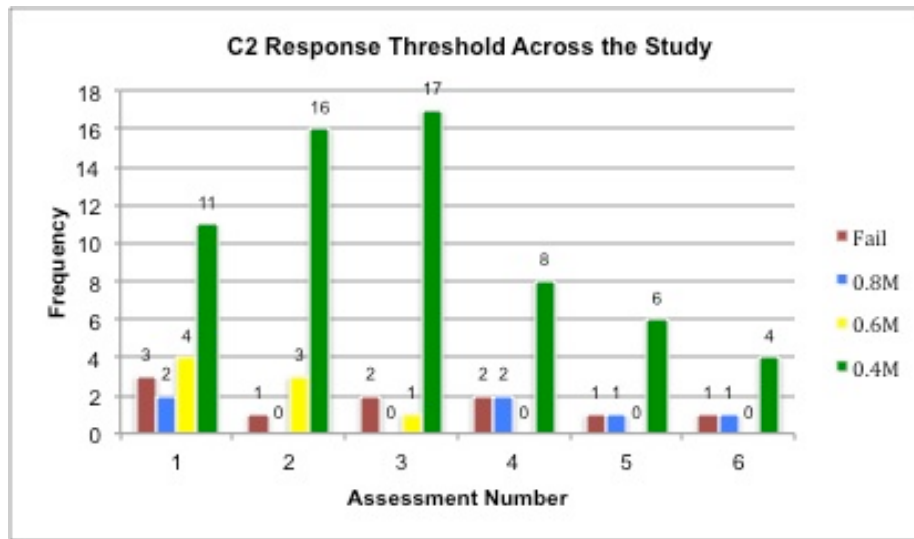
Figure 1: Agreement between improved or not improved C2 response threshold and change in PAS score



There were a total 51 instances where there was no improvement in C2 response threshold, 28 of these incidences occurred with no improvement in PAS and 23 of these incidences occurred with an improved PAS score. There were a total of 15 instances where an improved C2 response threshold was recorded. Eight of the 15 instances occurred with an improved PAS score and in seven instances PAS score was not improved. Of the total 15 incidences of improved C2 response threshold, seven occurred on the second assessment. Three incidences of improved C2 response threshold occurred on the third assessment. There were no incidences of improved C2 response threshold on the fourth assessment and there were three and two incidences of improved C2 response on the fifth and sixth assessment respectively (Table 2).

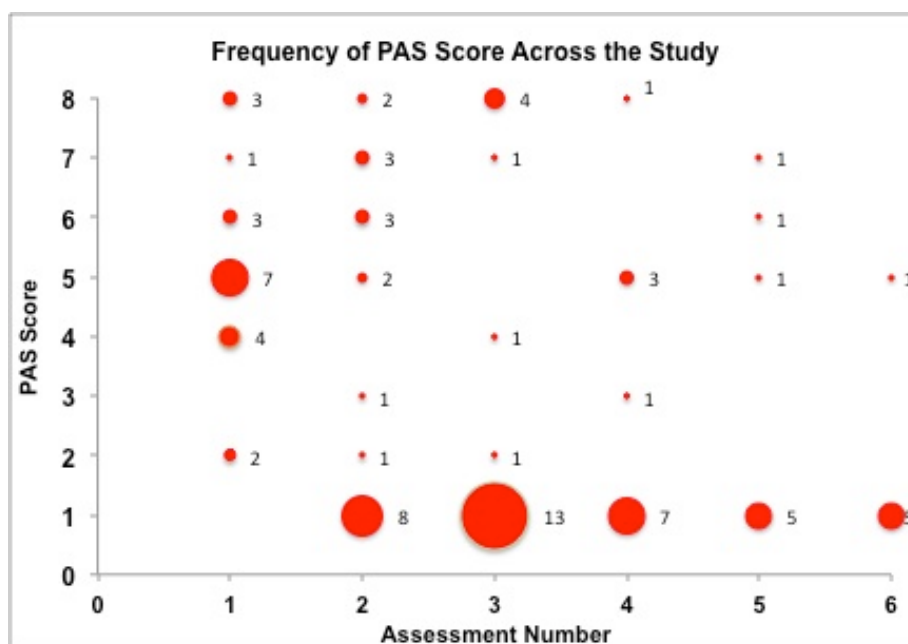
On initial and re-assessment C2 response threshold was recorded (Figure 2).

Figure 2: C2 Response Threshold Across the Study



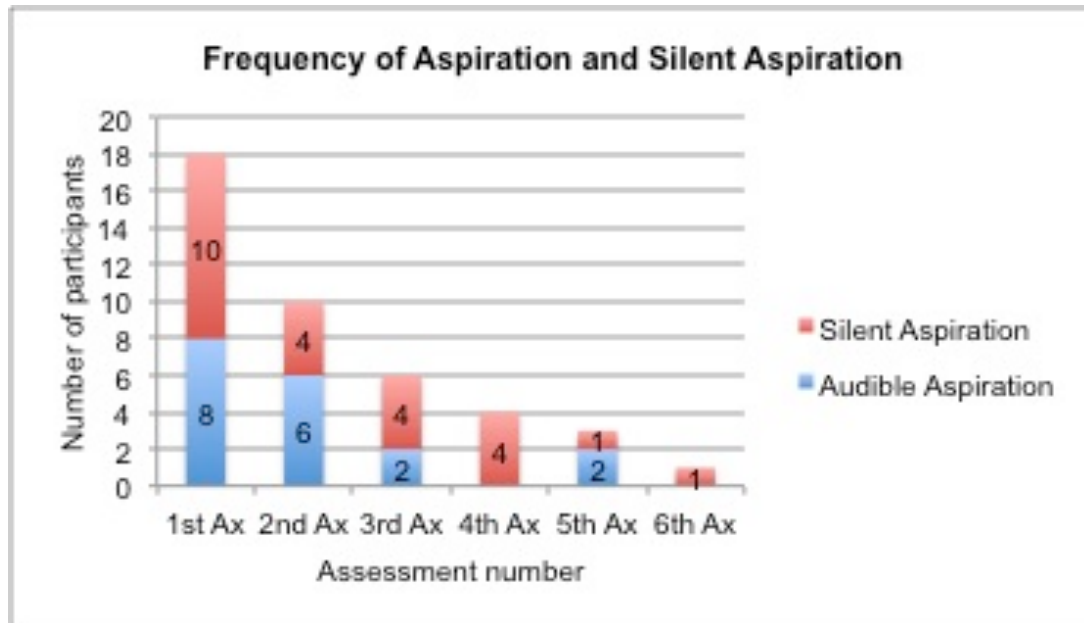
On initial and re-assessment PAS score was recorded (Figure 3). Figure 3 shows the frequency of PAS score at a given assessment. On initial assessment, seven participants had a PAS score of 5. On initial assessment a total of eighteen participants (90%) aspirated (PAS score of 4 or more) and ten participants silently aspirated (PAS score 5 and 8). On final assessment one (5%) participant had a PAS score of 4 or more.

Figure 3: PAS Score Across the Study



The frequency of aspiration and silent aspiration at each assessment is displayed in figure 4.

Figure 4: Frequency of Aspiration and Silent Aspiration



Ten participants were seen to silently aspirate on initial assessment when examined as a subgroup (table 3) due to the clinical pertinence of this subgroup. Four of these participants (5, 10, 16 and 20) demonstrated silent aspiration on their initial assessment, no silent aspiration on the second assessment (post 4 days), and there was an improved C2 response threshold (Appendix VI). In four cases (participants 2, 4, 12 and 18) silent aspiration occurred on the initial assessment, but did not occur on second assessment (post 4 days), and there was no change in C2 response threshold (C2 response threshold was 0.4M on initial and second assessment) (Appendix VI). There is one case (participant 9) where initially present silent aspiration resolved on second assessment and C2 response threshold increased (0.4M to 0.6M) (Appendix VI). Only one participant (participant 8) silently aspirated on initial assessment and was seen to continue to silently aspirate on second assessment, their C2 response threshold remained unchanged (0.4M) (Appendix VI).

There are eight occasions in the data where silent aspiration is recorded during the course of re-assessment having not occurred on the prior assessment (See table 4). There is only one incidence where this is associated with deterioration in C2 response threshold.

There were eight instances where audible aspiration was observed on thin fluid however, silent aspiration occurred on thickened fluids (Thickened Creamy Base Mildly Thick Nectar Flavor Creations Australia) (Appendix VIII). Eleven participants were seen to aspirate single sips of fluids on initial assessment. No participants were seen to aspirate puree on initial assessment (Appendix VIII).

Inter-rater reliability was tested. Percentage agreement between the two markers was high, 99% for C2 response threshold and a 98% mean for all PAS scores across consistencies (see table 5 for full results.)

6.0 Discussion

This pilot study is the first of its kind to utilize FEES and citric acid CRT to investigate the relationship between improvement in laryngeal cough reflex sensitivity and improvement in aspiration/penetration status in the acute stroke population. Nineteen of the 20 participants showed improved swallowing function during the study. Improvement in swallowing was defined as reduction in initial PAS score compared to final PAS score. However, only eight of the 20 participants showed improved cough reflex threshold. Improved cough reflex threshold was defined as reduction in initial cough response threshold compared to cough response threshold on final assessment. Four of the nine participants that silently aspirated on initial assessment and not on the second assessment had an improved C2 response threshold. Whilst swallowing and cough reflex sensitivity was seen to improve in the acute stroke population the relationship between the two was poor. The reason for this poor relationship may be due to the measures taken in this study. Improvement in cough sensitivity was compared to overall improvement in penetration/aspiration status. Although there could potentially be a relationship between these two, due to neural recovery patterns, the critical question is the relationship between cough sensitivity and specifically response to aspiration as opposed to general improvement in penetration/aspiration status. Whilst the relationship between improvement in laryngeal cough reflex sensitivity and improvement in aspiration/penetration status in the acute stroke population was poor in this study, the small sample population and methodological limitations, which are discussed further, prevent the null hypothesis from being conclusively accepted.

Previous clinical research utilizing cough reflex testing (Addington et al. 1999a; Addington et al. 1999b; and Addington et al. 2005) employed a protocol in which oral intake was resumed in stroke patients who have previously failed a CRT based on passing a repeated CRT test and clinical assessment. There are limited findings from this study that offer some support for this practice. Nine participants were seen to silently aspirate on initial assessment, and not on their second assessment. Four participants in this group did not reach C2 response threshold at 0.4 M on initial assessment.

However all four of these participants reached C2 response threshold at 0.4 M on the second CRT assessment. On second assessment three of the four participants had resolved aspiration and one participant had resolved silent aspiration but not aspiration.

6.1 Cough

The primary aim of this study was to investigate the agreement between change in C2 response threshold and PAS score in the acute stroke population. Whilst cough reflex sensitivity was seen to improve the relationship to improved PAS score was poor. Responses to CRTT may represent a slight flooring effect. There may have been subtle changes in cough reflex sensitivity threshold that were missed due to the lowest citric acid concentration being 0.4 M. Alternatively, this finding may accurately reflect the percentage of the study population that had intact laryngeal sensation on initial assessment. For these participants the stroke may not have affected laryngeal cough reflex sensitivity. Alternatively, impairment may have occurred but resolved by the time the participant was appropriate for assessment with oral intake. Addington et al (2005) proposed theory of “brainstem shock” (p.7) describe impairment of one or more of the following; the reticular activating system (RAS), respiratory drive or the laryngeal cough reflex. Given the RAS is responsible for regulating arousal and sleep wake cycle it is plausible that once participants were deemed alert enough (indicative of improved RAS function) for assessment, brainstem shock had resolved and therefore laryngeal cough reflex had also returned to normal threshold sensation. A study comparing cough reflex threshold immediately and again, when appropriate for swallow assessment, would answer this question. The possibility of rapid normalisation of cough reflex sensitivity presents an argument for early assessment in the form of nurse screening on admission to hospital. If “brainstem shock”(p.7) resolves rapidly, the delay in specialist dysphagia assessment being undertaken may result in CRT not being a valid measure for clinicians or might come in too late.

Previous research by Monroe (2010) reports that over 90% of healthy people were found to elicit cough at 0.8M citric acid concentration. Monroe (2010) concluded 0.8M citric acid concentration would be an appropriate level for clinical use. However this study demonstrated that in a sub-acute stroke population (<1 month) 90% (n18) had a cough response threshold of at least 0.4M citric acid concentration (figure 3). This finding provides support for reducing the citric acid concentration from 0.8M to at least 0.4M for clinical use.

There were seven incidents where cough response deteriorated on re-assessment. There are several possible explanations to explain deterioration in C2 threshold. Firstly, it may accurately reflect change in sensitivity of the cough reflex. Whilst factors such as alertness and presence of pneumonia were recorded in the study, factors such as state of oral hygiene which is known to affect cough reflex sensitivity (Watando et al, 2004) were not controlled for. Additionally, there may have been other factors that could have resulted in a deterioration in C2 threshold in this population that have not yet been investigated; e.g. placement of a nasogastric feeding tube, dehydration. Research on the variability of cough reflex threshold in the general hospitalised population is required. A second explanation for this variability leads us to question the reliability of the CRTT. A simple way to address this question would be to carryout repeated CRTT under strictly the same conditions in clinical and non-clinical populations. Multiple variables would have to be tightly controlled for in the clinical population.

The focus of much of the research on laryngeal cough reflex testing has been on the tests ability to reduce pneumonia rates (Addington et al. 1999a; Addington et al. 1999b; Addington et al. 2005; Miles, McLauchlan & Huckabee (*in progress*)). Recent studies have also looked at validating the CRT as a method of detecting silent aspiration against validated methods namely VFSS (Moore & Huckabee *in progress*) and FEES (Miles & Huckabee, *in progress b*). However, there appears to be an absence of research questioning whether CRT is a valid measure of laryngeal sensation responsible for the expiratory response or a more general measure of cough sensitivity. During the CRT, citric acid is

likely to not only reach the laryngeal cough receptors but also migrate to cough receptors throughout the tracheobronchial tree. It is likely that any test that uses nebulised mist will not only target cough receptors in the larynx but also those in the tracheobronchial tree, thus essentially testing the integrity of the Vagus nerve as opposed to specifically the ibSLN which obviously remains clinically pertinent to aspiration pneumonia risk. In order to investigate the validity of the CRT as a test of laryngeal cough reflex sensitivity, research directly comparing CRT with FEEST (Fiberoptic Endoscopic Evaluation of Swallowing with Sensory Testing) (Aviv et al, 2000) would be advantageous for this field of work.

All participants were able to complete the CRT without concerns of leakage that arise from the mouthpiece method. Several of the participants were unable to drink via a straw due to oral dyspraxia and/or facial weakness and would have likely not been able to carryout a CRT with mouthpiece administration. This further supports the use of a facemask method in the stroke population. Inter-rater reliability for C2 response threshold was 99% and 93% for judgment of cough strength (weak/strong). Whilst inter-rater reliability is strong for both observations it suggests that strength of cough may be more difficult to judge than mere presence. Therefore it would suggest training and regular Inter-rater reliability measuring on cough and cough judgment should take place along side the clinical use of CRT.

6.2 Dysphagia

Our data of documented aspiration are consistent with other studies that have reported similar rates of silent aspiration; (Daniels et al. 1998; Horner, Massey, Riski, Lathrop, & Chase 1988; Holas, DePippo, & Reading 1994). In agreement with previous studies (Gorden, Langton, Hewer, & Wade 1987; and Hamdy et al. 1998), the presence of aspiration was transient for most participants in this study. Reduction in incidence of aspiration was most substantial between the first and second assessment with resolution in all but one participant by the final assessment. This participant had a

past medical history that included previous dysphagia. Whilst on admission to the trial the participant had reported the previous dysphagia had fully recovered and an unmodified diet was being taken, the aspiration observed cannot be conclusively attributed to the most recent stroke.

There were 35 incidences where PAS score was recorded to not improved on re-assessment. In 16 of these cases, PAS score had in fact deteriorated, as opposed to simply not improved on re-assessment. This may well accurately reflect deterioration of swallowing function; factors such as alertness are known to effect swallowing function and alertness is known to often fluctuate. Additionally, this finding might highlight what we know already about instrumental assessment, which is it provides a transient capture of swallowing function only, therefore the swallowing may not have deteriorated from previous assessment but the full degree of the dysphagia may not have been identified on previous assessment. The provision of only three boluses for each food and fluid consistency in this study may have contributed to this finding. The relatively high incidence of PAS score deterioration on re-assessment reinforces the need when making clinical decisions to carefully consider instrumental assessment findings. Recommendations on suitability of commencing oral intake should be made based on the patient's clinical presentation as a whole, not just instrumental assessment findings.

There were eight instances where audible aspiration was observed on thin fluid however silent aspiration occurred on thickened fluids. This scenario was seen in six participants and raises several important issues. Firstly, the properties of cough receptor stimuli and critically the use of thickened fluids in dysphagia management. This finding may suggest that there are fundamental differences in the way cough receptors react to presence of different fluids on the vocal fold in the acute stroke population. These differences may arise due to potentially different thermal, viscosity and chemical properties of the aspirated material. Clinically, the termination of audible aspiration on thin fluids with the introduction of thickened fluids is often attributed to resolution of aspiration. However, this study has shown that in at least 8 separate incidences this was not the case and in fact the cessation of

coughing reflected silent aspiration as opposed to resolution of aspiration. Reliance on this false belief could have in fact left the patient at much higher risk of developing an aspiration pneumonia than if had they continued to audibly aspirate thin fluid. This raises serious questions as to the appropriateness of prescribing thickened fluids based on bedside assessment alone. This finding supports the view that thickened fluids should only be prescribed after their potential risks and benefits have been fully evaluated on instrumental assessment. There were no incidences where thin fluids were aspirated silently and thickened fluids aspirated audibly. The limited sample size, limited bolus trials and the potential for an order effect (thin fluids were always trialled before thickened) prevent significant conclusions being drawn. However these findings in addition to Robbins & Hind (2008) results which reported more frequent incidence of urinary tract infection and dehydration with thickened fluid use, presents strong support for further research into the area of thickened fluid use in the post-stroke population.

The Penetration Aspiration Scale (Rosenbek, 1996) was used in this study to quantify the participants' aspiration/penetration status. One of the key benefits of this scale is that it is validated. However there are limitations to its usefulness in this study. Firstly, a score of eight is given if material enters the airway, passes below the vocal folds, and no effort is made to eject from the airway. A score of five suggests an improvement or reduction in aspiration/penetration and indeed to score five the material is seen only to contact the vocal folds, however the material is not ejected from the airway. Whilst the assumption is there is an improvement between a score of eight and five, both scores indicate silent aspiration. Given the aim of this study was to look at improved swallowing in the context of improved laryngeal sensation a PAS score change from eight to five does not reflect improvement in terms of sensation. Indeed one would anticipate that a patient would continue to fail a CRT with a PAS of eight and five. Secondly some of the scores are open to interpretation. The score five is given when "material enters the airway, contacts the vocal folds and is not ejected from the airway" it is not stipulated in this score whether or not there was an absent cough or their cough was a cough but it was ineffective. This distinction is critical when considering laryngeal sensation. A more

useful scoring system may be to simply record aspiration/no aspiration, and cough response to aspiration present/absent.

7.0 Conclusion

This pilot study reported no significant agreement between improved laryngeal cough reflex threshold and improved PAS scores in the acute stage. Whilst this study shows that both laryngeal and cough reflex thresholds and PAS scores improve, an association between the two was not identified. However, significant conclusions are difficult to draw due to the small sample size and potential ceiling effect of the CRT. This study identifies incidence of silent aspiration in the acute post-stroke dysphagia population consistent with existing empirical research findings. This study also raises several questions about the use of thickened fluids in the acute post-stroke population.

Further large-scale research is required in order to further investigate whether it is appropriate to instate oral intake in the known silent aspiration population based on passing a previously failed CRT. In order to directly address this question, future research assessing CRTT and response to aspiration in the post-stroke silent aspiration population is required. This current research does however raise many interesting questions as well as highlight the complex nature of cough and swallow recovery and the need for further research in this area, particularly with the increasing routine clinical use of CRT in the post-stroke population.

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Information Sheet

Appendix I



INFORMATION SHEET

Research Title:

Cough reflex testing in swallowing assessment.

Primary / Principal Researcher:

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Co-Investigators:

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MSc Student, University of Canterbury

Speech and Language Therapy

North Shore Hospital, Waitemata District Health Board

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Dept of Otolaryngology, North Shore Hospital,

Introduction and aims of the project:

You/ your whanau member/ friend has been asked to participate in a research project that will evaluate the use of a cough test as part of a swallowing assessment. You have the right not to participate in the study, or subsequently withdraw from this study at any time.

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Any decision not to participate will not affect current, continuing or future health care at this or any other health care facility.

In many patients with swallowing problems the ability to cough when food enters the lungs will be impaired. Currently there is no way to reliably identify patients who have no cough and therefore no way of protecting their airway if food/drink slips down the wrong way (aspiration). The data from this study will be used to develop a method of identifying these 'at risk' patients, and hence improving their management.

The aim of this project is to validate a cough test against accepted measures of swallowing and sensation in the throat. The cough test involves placing a facemask over the nose and mouth, and then quietly breathing in a mist that contains a substance called citric acid. This substance may make you cough. Citric acid has been used for the purpose of eliciting cough since the 1950s, with no adverse effects. The assessment of aspiration and sensation in the throat will involve the use of the well-established test called 'flexible endoscopy'. This involves looking at your throat with a camera through a small tube placed in your nose. This assessment is part of routine clinical care for many patients and may be recommended if you participate in the study or not. If your swallowing or cough reflex is identified as being impaired as a result of a new stroke you will be reassessed using the cough test and flexible endoscopy. Reassessment will take place every four days for up to 3 weeks from your first assessment. Further reassessment will be discontinued before 3 weeks if safe swallowing and a normal cough reflex is identified on re-assessment during this period. Your ward speech language therapist will be provided with the results of all your assessments and will then use this information to plan your treatment.

Participant selection:

You/ your Whanau member/ friend has been identified as a potential participant for this study since being referred to a speech-language therapist with suspected or confirmed swallowing difficulties. Upon your consent, you will be selected for this study. The study will include a total of 100 participants. We acknowledge that you may wish to discuss this project with your Whanau before consenting.

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The research procedure:

If you agree to participate in the study, the following will occur:

1. Once you/ your Whanau member/ friend has signed the consent form to participate in the study, you will be seen by the researchers for a number of assessments.
2. **Cough Reflex Testing-**
 - i) This test takes a maximum of 10 minutes to complete.
 - ii) You will be given a facemask, which is attached to a device that turns water into a mist, called a nebuliser.
 - iii) A small quantity of citric acid (of various doses) will be mixed into water. You will be asked to quietly breathe in through the mask for a period of 15 seconds
 - iv) The mist you inhale may make you feel like coughing. You will be asked to cough if you feel the need to cough, but not to if you don't.
 - v) At each dose, the test will be repeated two more times to evaluate how consistently you cough when you breathe in the mist.
 - iv) This will be repeated for 3 different doses of citric acid (0.8M, 0.6M, 0.4M) to determine what concentration of citric acid makes you cough.
3. **Flexible Endoscopic Study of Swallowing with Sensory Testing-**

This test takes a maximum of 20 minutes to complete.

 - a. One of the researchers, trained in this procedure, will place a flexible endoscope through your nose. This allows the clinicians to view the inside of your throat and voice box. The scope sits above the voice box during the test.
 - b. You will be asked to drink and eat small quantities of food and liquid. Your researcher will support you through the assessments in accordance with the hospital's Tikanga Best Practice Policy and the option of a Karakia prior to assessment will be offered
 - c. If you did not cough at the 0.8M concentration of citric acid in your cough test, small puffs of air will also be sprayed into your throat to allow the clinicians to observe your response. If you do not response to the air, a small amount of water (0.5ml) will be sprayed into your throat also.

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4. If you have had a stroke and food/ fluid goes into your airway or your cough reflex is weak on your first assessment, you will be asked to repeat the assessments every 4 days to watch for improvement. This will continue for 3 weeks or until your swallow and cough have improved.
5. If you consent to the study, your ward speech-language therapist will be provided with the results of the assessments to help in the management of your swallowing difficulties.

Risks and Benefits:

It is possible that your overall outcomes may be improved because your ward therapist will be provided with more information about your cough, swallowing and sensation in your throat. There are no documented adverse side effects of the cough test. Nevertheless, it will be performed by trained research clinicians who will monitor you for any difficulty during the test.

The other test, (Flexible Endoscopic Study of Swallowing with Sensory Testing) is considered a safe, well-recognised assessment tool. When carried out by experienced clinicians side effects are rare but may include nosebleed, and fainting. Some patients experience discomfort as the scope is inserted.

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Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

Research findings will be presented at international research meetings and submitted for publication in peer-reviewed journals. Additionally, research findings will be made available to the local medical community through research presentations and regional forums. However, no material that could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the speech and language therapy departments at the hospital or will be stored on password-protected computers. Research data will be stored for a period of ten years after data collection is complete, at which time they will be destroyed. With your permission, data from this study may be used in future related studies, which have been given ethical approval from the Northern Y Ethic Committee.

Results:

If requested, you will be offered copies of the publications that arise from this research. However, you should be aware that a significant delay may occur between completion of data collection and completion of the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the lead investigator.

Questions:

You may have a friend or whanau support to help you understand the risks and/or benefits of this study and any other explanation you may require.

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Please contact your speech and language therapist if you require any further information about the study. Alternately, the primary researchers listed on the front page of this information sheet can be contacted during work hours at the numbers provided.

If you need an interpreter, this can be provided.

To ensure ongoing cultural safety Nga Kai Tataki - Maori Research Review Committee Waitemata DHB encourage those who identify themselves as Maori and who are participating in health research or clinical trials to seek cultural support and advice from either Mo Wai Te Ora – Maori Health Services or their own Kaumatua or Whaea. For assistance please contact the Services Clinical Leader for Mo Wai Te Ora – Maori Health on 09 486 1491 ext: 2324 or the Maori Research Advisor on 09 486 1491 ext: 2553

If you have any queries or concerns about your rights as a participant in this study, you may wish to contact a Health and Disability Advocate, telephone: Auckland Central: 09 525 2700 or 0800 555 050. Free Fax (NZ wide): 0800 2787 7678 (08002SUPPORT). Email (NZ wide): advocacy@hdc.org.nz.

Consent Form

Appendix II



Cough Reflex Testing in Swallowing Assessment			
English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I, _____, have read and I understand the Information Sheet about taking part in this study designed to collect information about the usefulness of cough reflex testing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had this project explained to me by _____.

- I understand that taking part in this study is voluntary (my choice) and that should I withdraw from the study, this will in no way affect my current, continuing or future health care. I understand that I can withdraw from the study at anytime during the assessment phase. Once my assessments are completed, my details will be anonymously collated and will no longer be able to be identified or withdrawn.

Cough Reflex Testing in Swallowing Assessment

- I understand my assessments will be recorded for the purpose of analysis only. Recorded material will be stored in a locked office and on a password-accessed computer.
- I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
- I understand that the investigation will be stopped if it should appear harmful to me and I know who to contact if I have any side effects to the study or have any questions about the study.
- I understand the potential risks of participation in the study as explained to me by the researcher.
- I have had time to consider whether to take part.

I wish to receive a copy of the results.

YES / NO

Address to send results: _____

I, _____ hereby consent to take part in this study.

Date _____

Signature _____

Signature of researcher _____

Name of researcher _____

Name of primary researchers and contact phone numbers:

Name: Anna Miles (021 137 1658), Mary McFarlane (021 951 277), Dr. Jacqui Allen (09 4861491 ext 2811), Dr. Maggie-Lee Huckabee (03 378 6070)

Consent Form by proxy

Appendix III



STATEMENT BY RELATIVE/FRIEND/WHANAU

Cough Reflex Testing in Swallowing Assessment			
English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

Study title:	Cough Reflex Testing in Swallowing Assessment
Principal investigator:	Anna Miles
Participant's name:	

I have read and I understand the information sheet for people taking part in the study designed to collect information about the usefulness of cough reflex testing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I believe that _____ (participant's name) would have chosen and consented to participate in this study if he/she had been able to understand the information that I have received and understood.

- I understand that taking part in this study is voluntary. I understand that my friend/relative can withdraw from the study at anytime during the assessment phase. Once his/her assessments are completed, his/her details will be anonymously collated

Consent Form by proxy

Appendix III

and will no longer be able to be identified or withdrawn. This will not affect his/her continuing health care.

- I understand that his/her participation in this study is confidential and that no material that could identify him/her will be used in any reports on this study.
- I understand his/her assessments will be recorded for the purpose of analysis only. Recorded material will be stored in a locked office and on a password-accessed computer.
- I understand that the treatment will be stopped if it should appear to be harmful (**if applicable**).
- I understand the compensation provisions for this study (**if applicable**).
- I know whom to contact if my relative/friend has any side effects to the study or if anything occurs which I think he/she would consider a reason to withdraw from the study.
- I know whom to contact if I have any questions about the medication of the study.

This study has been given ethical approval by the Northern Y Ethics Committee. This means that the Committee may check at any time that the study is following appropriate ethical procedures.

I/my relative/friend would like a copy of the results of the study.

<input type="checkbox"/>	Yes	<input type="checkbox"/>	No
<input type="checkbox"/>	Yes	<input type="checkbox"/>	No

I believe my relative/friend would agree to his/her GP being informed of his/her participation in this study.

Signed:

	Date:	
--	-------	--

Printed name:

Relationship to participant:

Address for results:

STATEMENT BY PRINCIPAL INVESTIGATOR/CO-INVESTIGATOR

I _____ (*name of investigator*) declare that this study is in the potential health interest of the group of patients of which _____ (*name of participant*) is a member and that participation in this study is not adverse to _____ (*name of participant*)'s interests.

Consent Form by proxy

Appendix III

I confirm that if the participant becomes competent to make an informed choice and give an informed consent, full information will be given to him/her as soon as possible, and his/her participation will be explained.

If the participant makes an informed choice to continue in the study, written consent will be requested and if the participant does not wish to continue in the study, he/she will be withdrawn.

Signed:

Date:

(Principal Investigator/Co-investigator)

If applicable at a later date:

I _____ (*participant*) having been fully informed about this study agree to continue taking part in it.

Signed:

Date:

(Participant)

Independent Clinician Statement:

I confirm that participation in the study is not adverse to _____ (*participant*)'s interests.

Signed:

Date:

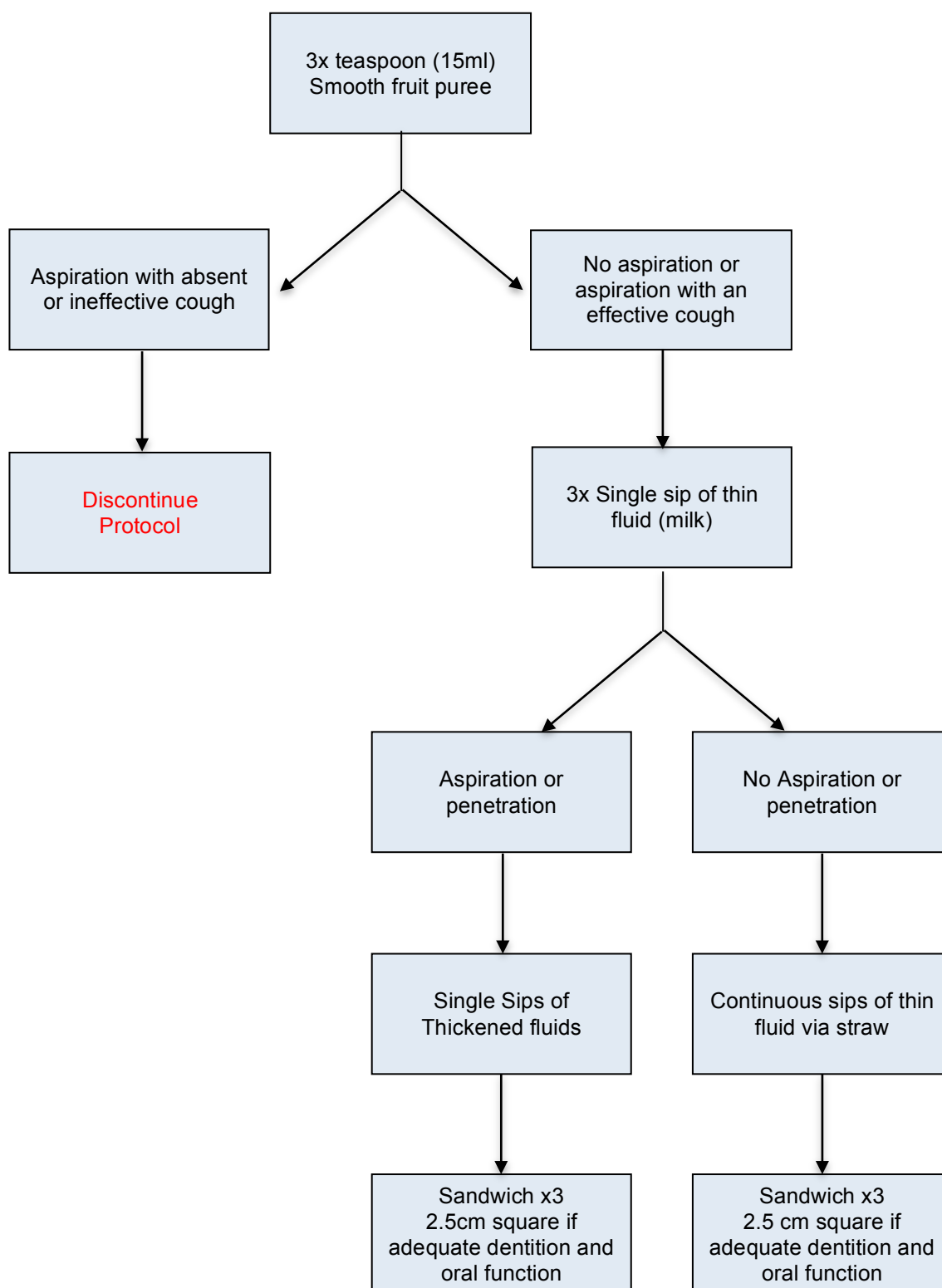
Name of primary researchers and contact phone numbers:

Name: Anna Miles (021 137 1658), Mary McFarlane (021 951 277), Dr. Jacqui Allen (09 4861491 ext 2811), Dr. Maggie-Lee Huckabee (03 378 6070)

Fees Protocol

Appendix IV

FEES Study Protocol



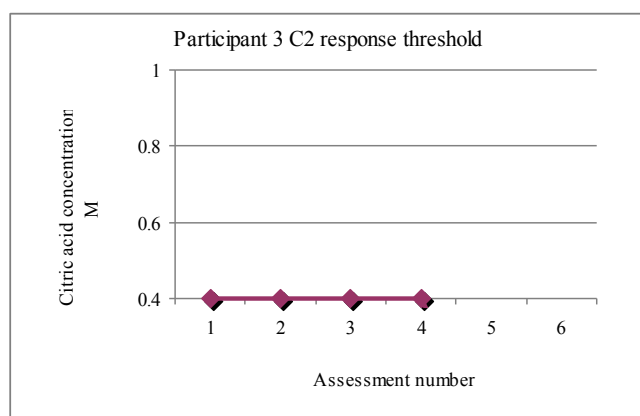
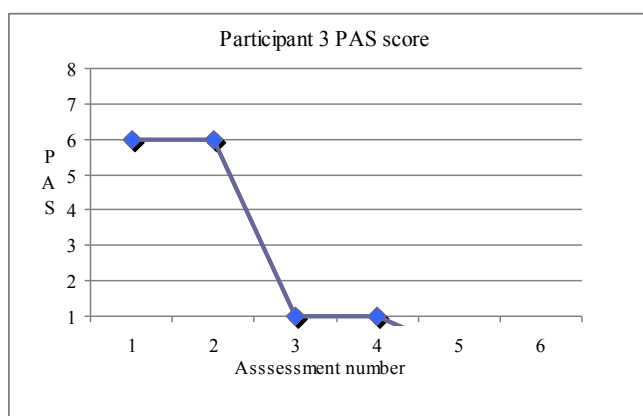
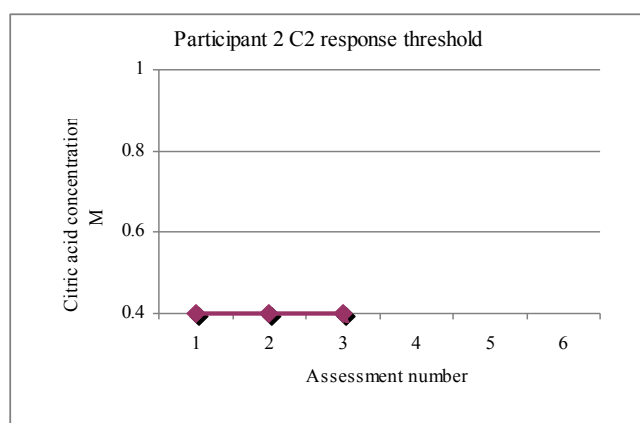
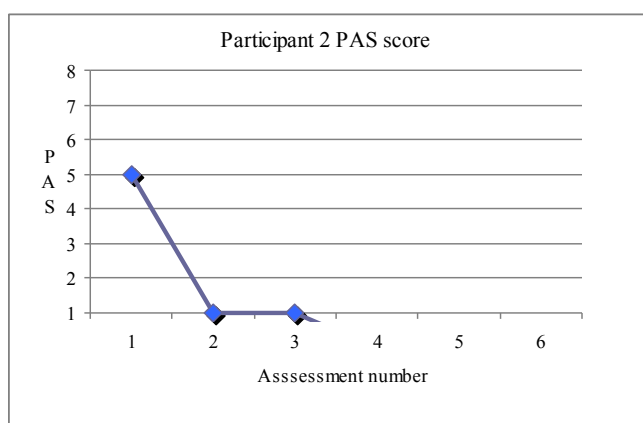
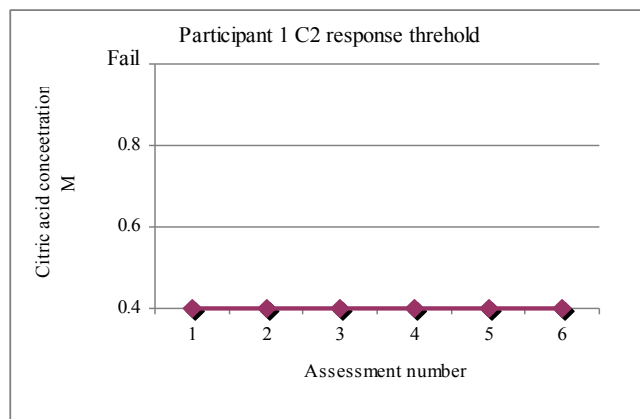
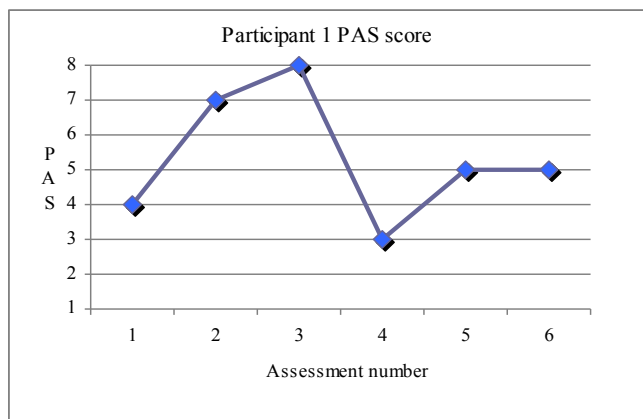
Eight Point Penetration-Aspiration Scale**Appendix V****Eight -Point Penetration-Aspiration Scale. Rosenbek, et al (1996)**

Score	Description of Events
1	Material does not enter airway.
2	Material enters the airway, remains above the vocal folds, and is ejected from the airway.
3	Material enters the airway, remains above the vocal folds, and is not ejected from the airway.
4	Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5	Material enters the airway, contacts the vocal folds, and is not ejected from the airway.
6	Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.
7	Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort.
8	Material enters the airway, passes below the vocal folds, and no effort is made to eject.

Participants Individual Graphs of C2 Cough Threshold and Overall PAS Score

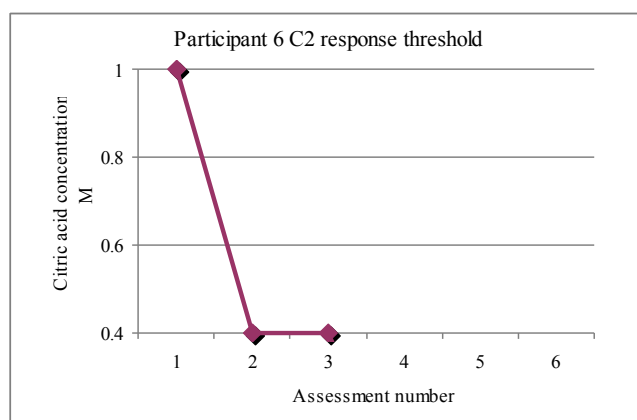
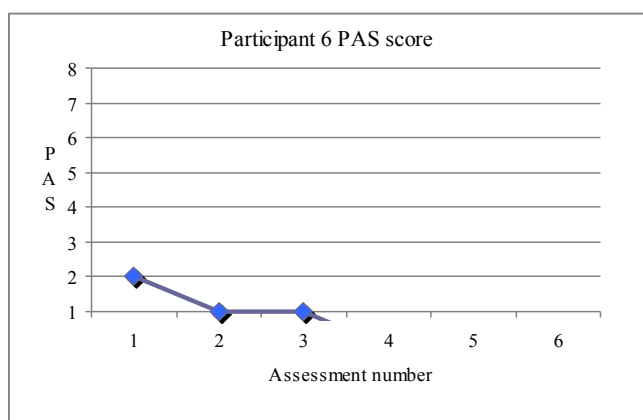
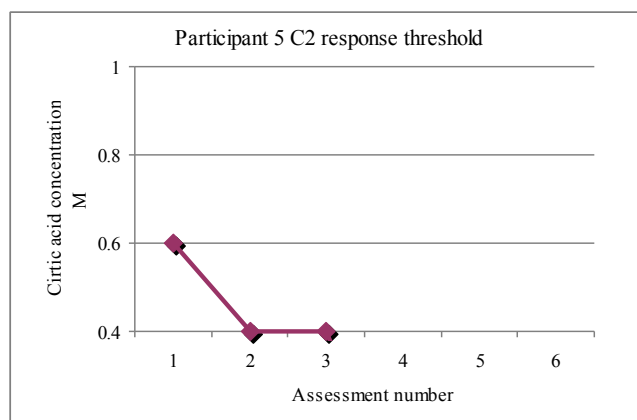
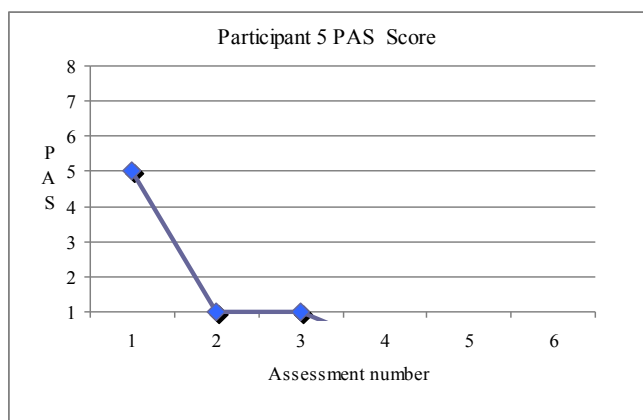
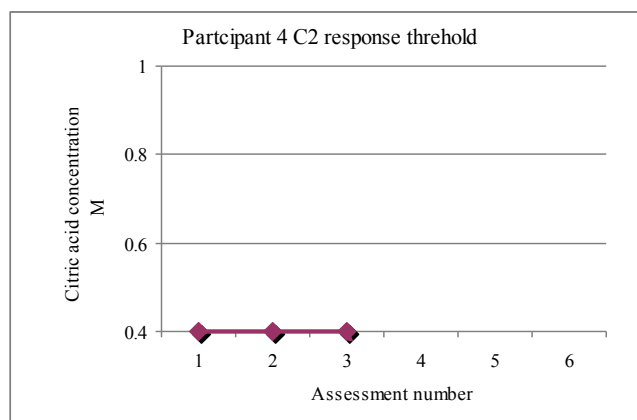
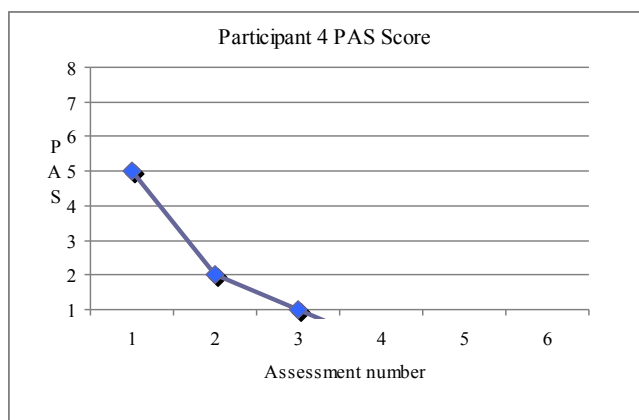
Appendix VI

Participants Individual Graphs of C2 Cough Threshold and Overall PAS Score



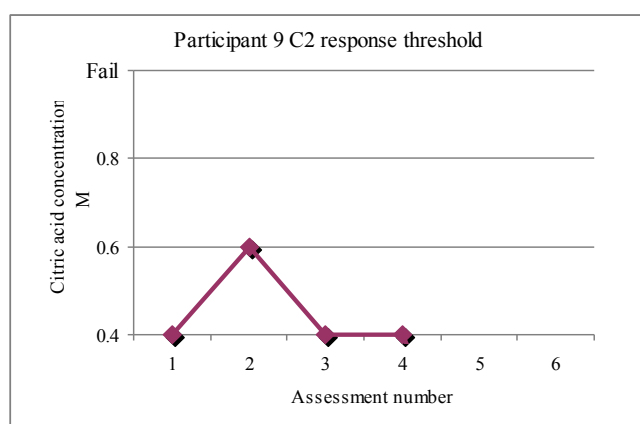
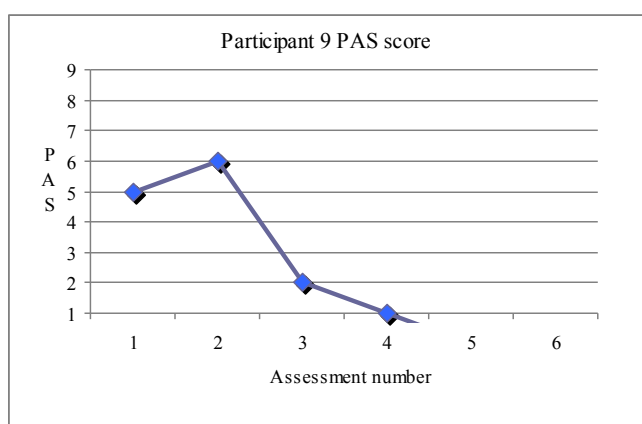
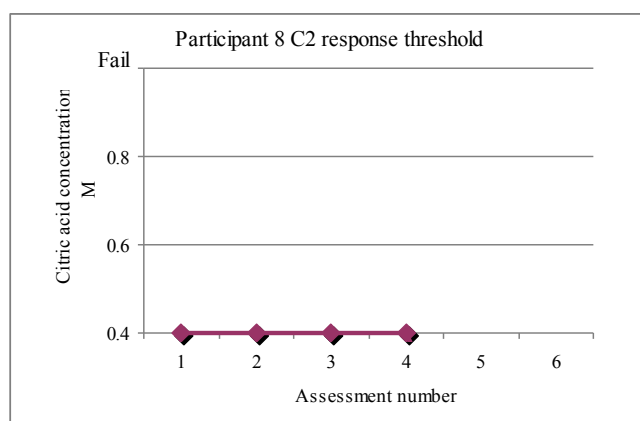
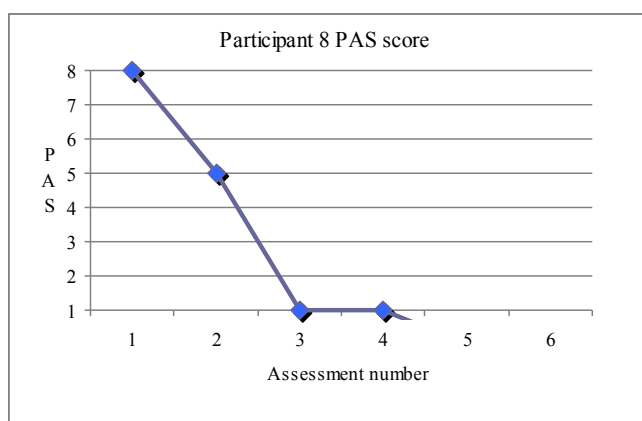
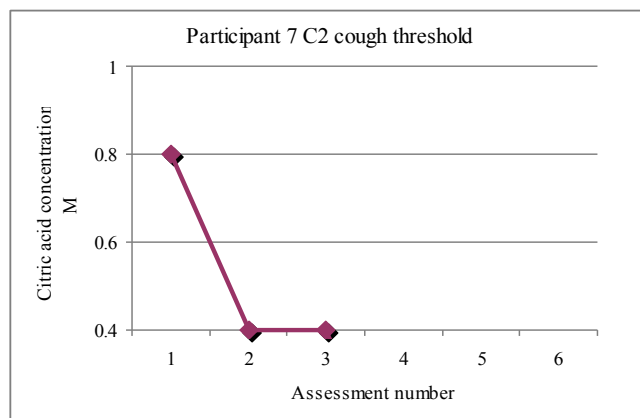
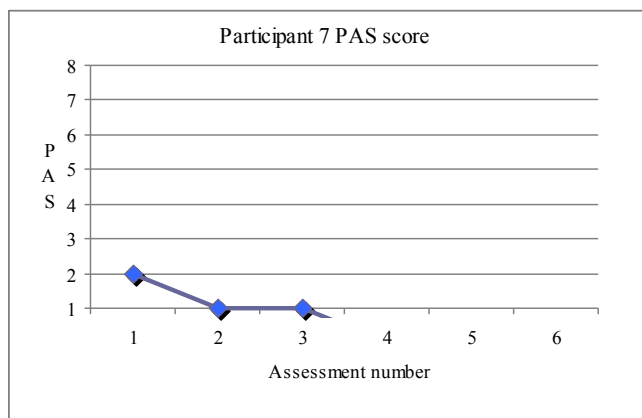
Participants Individual Graphs of C2 Cough Threshold and Overall PAS Score

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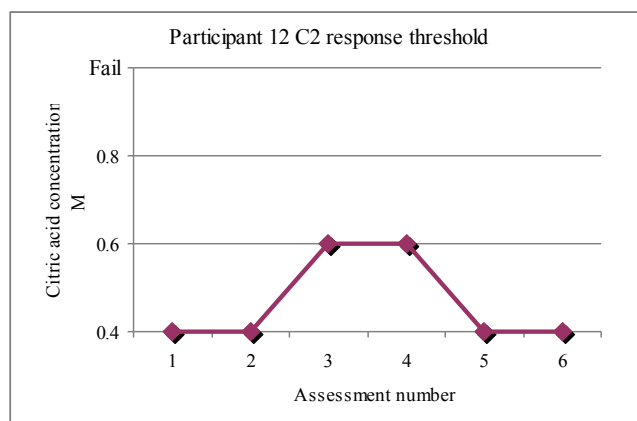
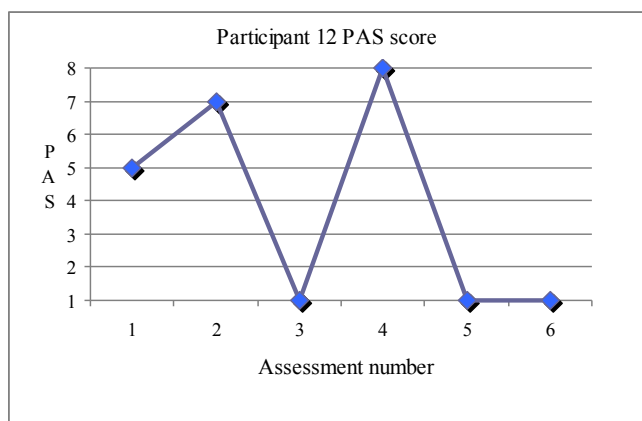
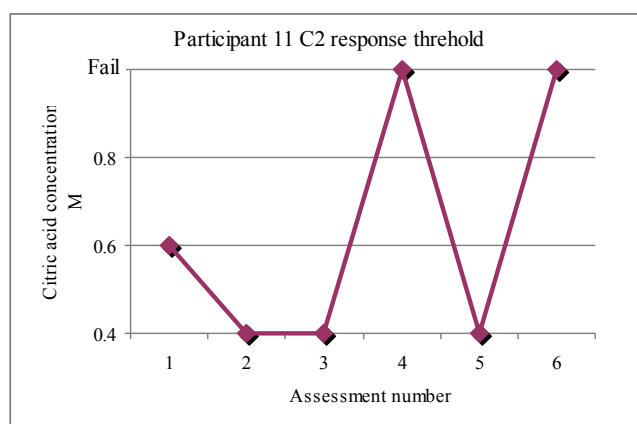
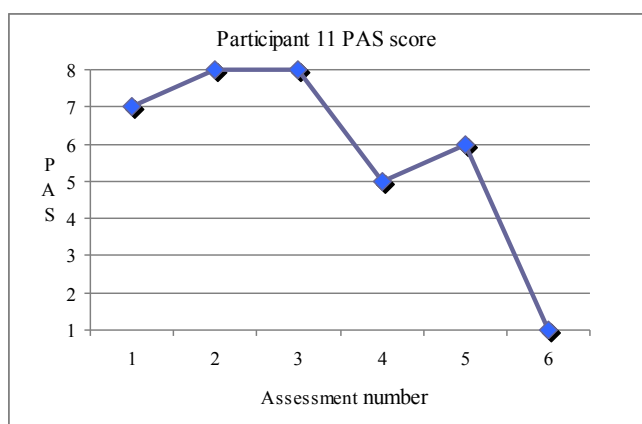
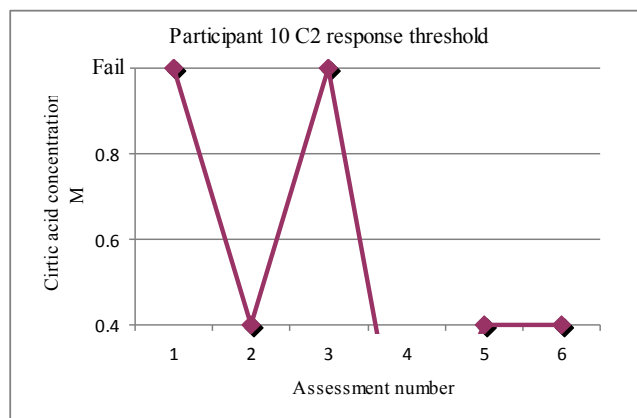
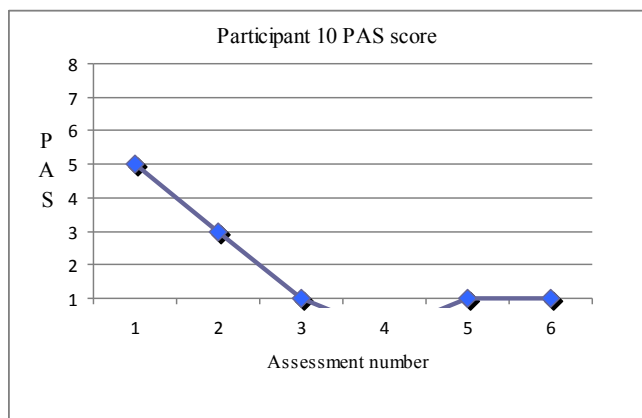
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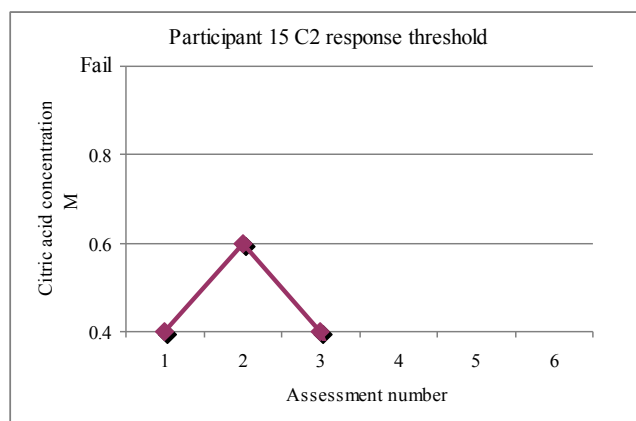
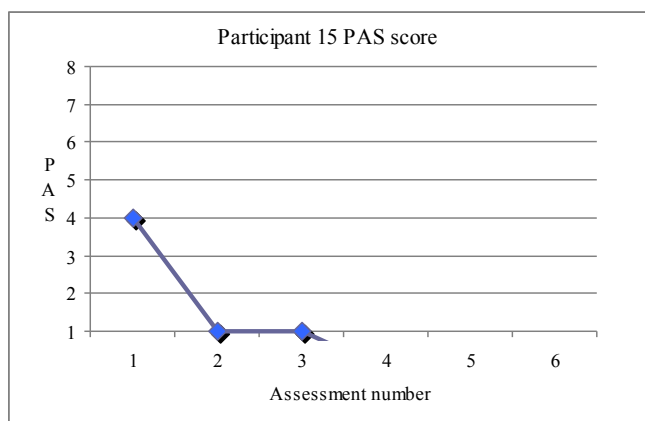
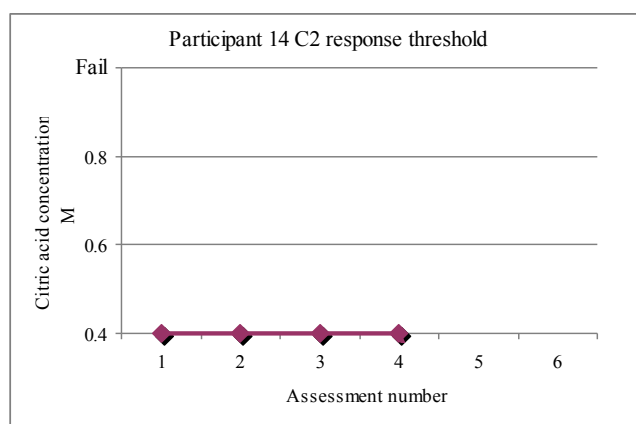
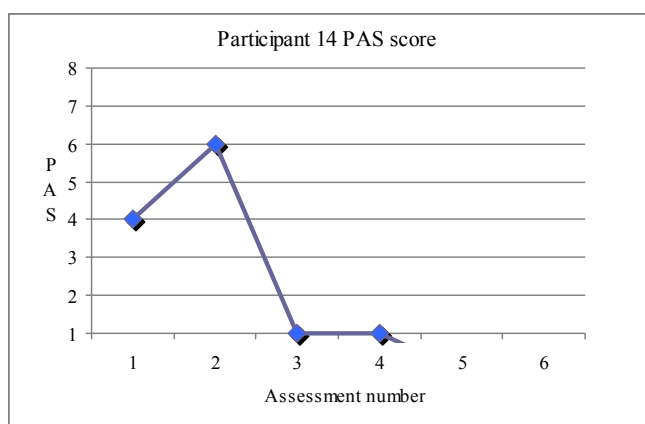
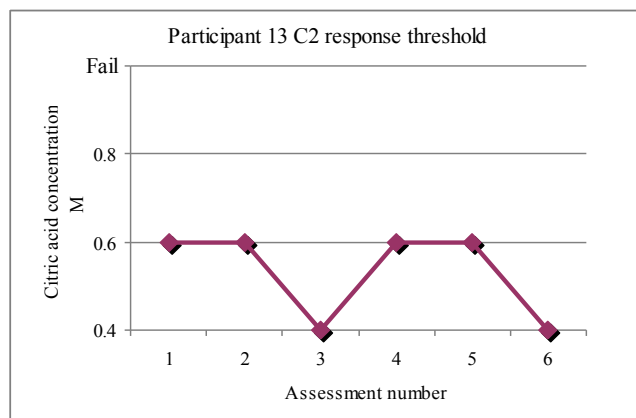
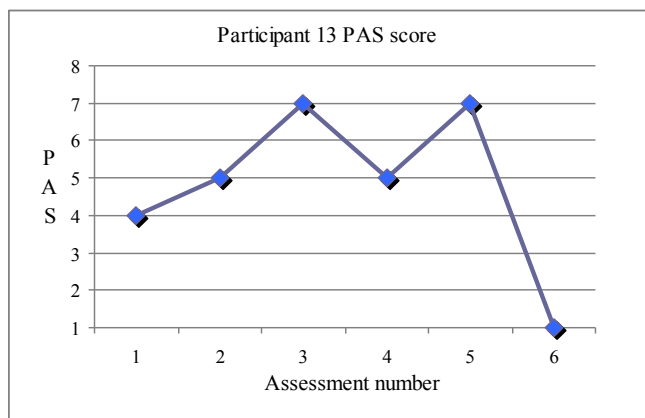
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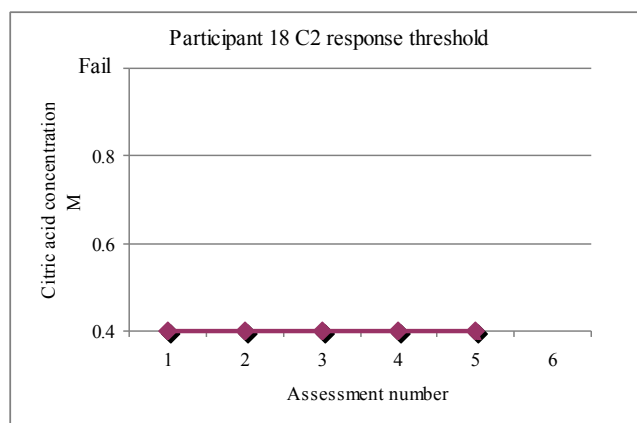
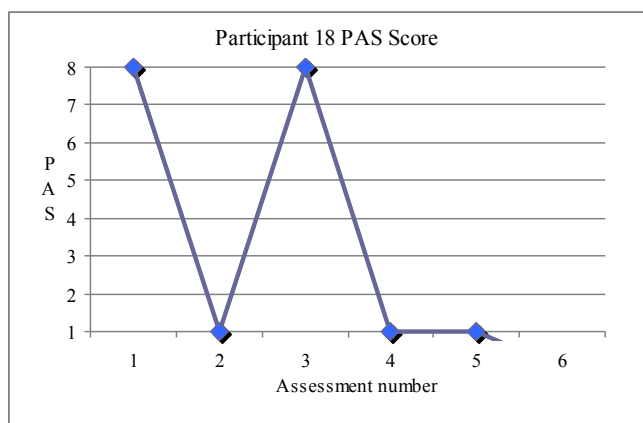
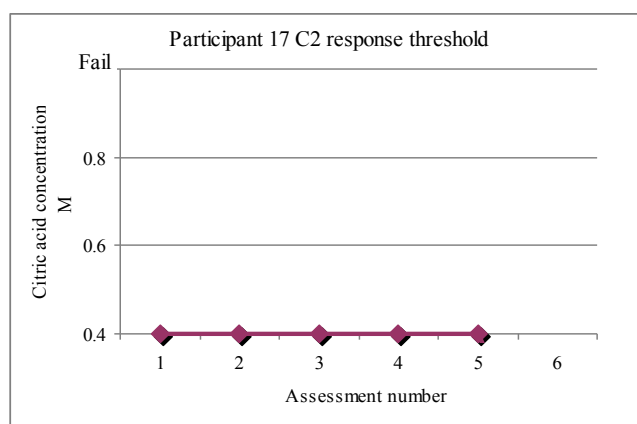
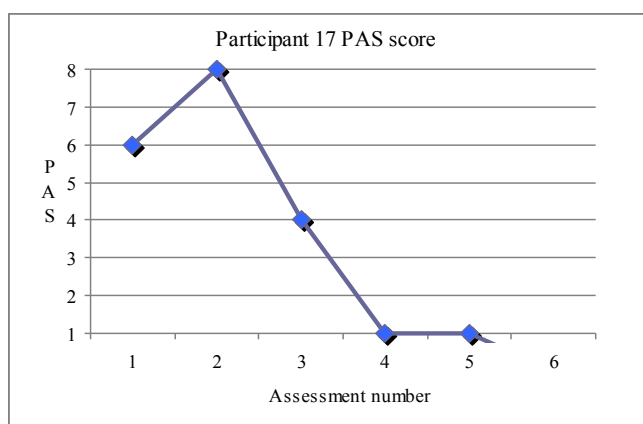
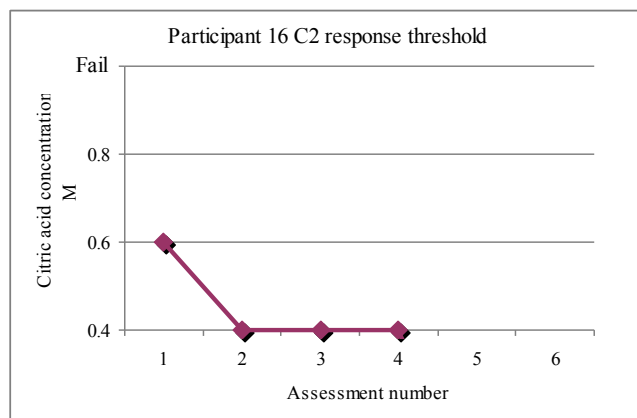
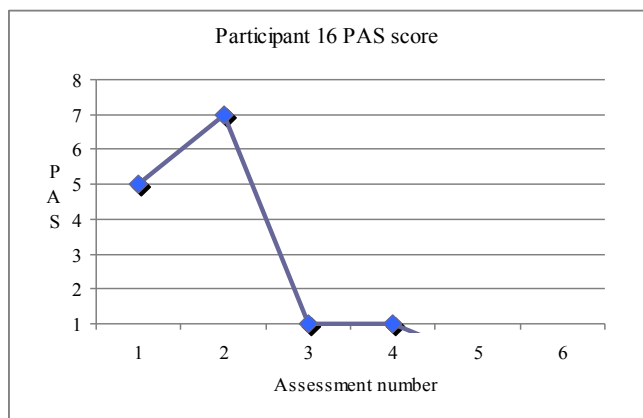
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